

RECENT ADVANCES IN HUMAN NUTRITION

**With a number of invited contributions
on special subjects**

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GENERAL REVIEW OF TRENDS

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CHAPTER 1

INTRODUCTION

IN a symposium on Significant Trends in Medical Research⁷¹ the author⁴⁴ reviewing research in clinical nutrition for the decade commencing 1950 drew attention to the rediscovery by clinical medicine and public health of amino acids and fatty acids, interest in which had, up to 1950, largely been submerged by an almost exclusive preoccupation with vitamins on the part of clinicians and public health workers.

The decade commencing 1960 promises new trends in human nutritional science. Their application to clinical medicine is likely to be both interesting and disconcerting; interesting because it is apparent that many aspects of man's mixed diet must be related to his long-term experience of health and disease; disconcerting because the uncertain implications of many advances will provide fresh ammunition for the food quacks. Orthodox medicine has ignored the food nostrums of quacks on the fallible philosophy that man, being an omnivorous animal, merely has to eat enough of a reasonably mixed diet to obtain his "recommended allowances of nutrients" while avoiding an excess of "empty calories" which will produce obesity. It has been assumed that the body is capable of eliminating any reasonable excess quantity of low-calorie nutrients and adapting itself to almost any balance of foodstuffs without being temporarily or permanently affected. It seems clear in 1960 that this optimistic estimate of the adaptability of the human constitution can no longer be accepted. Apart from short-term effects it seems likely that man's constitution is determined in part by his habitual food habits. This subject is dealt with briefly below under the heading *Diet and Constitution*. The subject is further taken up in Ch. 14 under the heading *Long-term Cumulative Effects of Diet*. It is a central theme of this book that constitution is determined in part by habitual diet and that therefore habitual diet must be considered in discussing the ætiology of a large group of diseases of uncertain and multiple ætiology which includes some of the major degenerative diseases of middle life. For Western medicine this may be the most important lesson coming from the study of clinical nutrition to influence thought in the 1960s.

The Scope of Clinical Nutrition. The field of nutrition, and even of clinical nutrition, is so wide that it interdigitates with every other medical discipline. This merely emphasizes that food is a fundamental necessity of life, and healthy food of healthy life. In the last resort good nutrition is indistinguishable from good health. This relationship is two-way and a breakdown at either end leads to a vicious circle of ill-health and malnutrition. This will be discussed especially in the section on malnutrition and diarrhoea, but the vicious circle principle is valid in every system of the body.

To narrow the scope of the book it has been decided to concentrate on the effects of dietary malnutrition; namely upon that half of the circle which runs from unsatisfactory food to disorder of bodily systems (in distinction from that half of the circle which runs from disordered systems through faulty appetite, digestion, assimilation, metabolism and excretion back to unsatisfactory food). In a book on clinical nutrition we cannot avoid consideration of those disorders which are conditioned, even when a good diet is readily available, by the mechanisms listed, but the discussion will return always to a dietary orientation. Only in this way can we avoid expanding the monograph into a textbook of medicine.

World Nutrition. Although the international public health aspects of malnutrition are not strictly within the purview of this book they cannot be ignored. Every clinician, even in the developed regions, is aware that there is a world problem of food in relation to population growth. Clinicians in underdeveloped regions are pressingly aware of the problems of malnutrition, undernutrition and even famine and starvation. They cannot feel an urgent interest in the possible long-term effects of diet on constitution and degenerative disease so long as these more urgent problems surround them daily and determine a community life expectation so short that the degenerative diseases are not likely to represent a community problem. Their colleagues in the developed regions can no longer live in an ivory tower because of the "internationalization" of the world. As the underdeveloped regions develop, the satisfaction of their pressing needs for the protective foods such as good quality proteins and vitamins may threaten the "plenty" of the developed regions. The "recommended allowances" of the privileged nations are already challenged as unrealistic or unattainable in the underdeveloped regions. The leaders of the relevant specialized international agencies (FAO, WHO, UNICEF) are saddled with a dilemma; are the recommended allowances of, say, the U.S.A., unnecessarily generous or must the rest of the world be satisfied

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indefinitely with allowances which are suboptimal for health. Clinicians in the developed regions are vitally concerned in the first alternative. If the recommended allowances are overgenerous does their application contribute to any form of overnutrition? If so, should they be reduced? (Ch. 11). Alternatively, "would a scaling-down of these allowances undermine reasonable body reserves and contribute to impaired vitality with increased susceptibility to infective and other acute diseases in the present (see Ch. 29 on Nutrition and Infection) or to impaired constitution and increased liability to degenerative disease in the future? (See Ch. 14 on Constitution and Degenerative Disease). If the latter alternative be right then the conclusion is of practical importance for the clinicians of the underdeveloped regions and to the public health and nutrition administrators of the specialized nutrition agencies of UNO and of individual nations.

For these reasons the author has included a section in Ch. 16 on World Population Growth and Food Supplies and has invited a contribution from WHO and FAO (Ch. 33).

Geographical Pathology. In Cape Town Nature has provided a unique natural experiment. It consists in the juxtaposition of three racial groups living in the same well-localized geographic and climatic environment, but differing markedly in their socio-economic status and in the incidence of undernutrition, malnutrition, and "social diseases" such as tuberculosis, syphilis and infantile diarrhoea. Interracial studies in this area and studies in geographical pathology throughout the African continent have led to some fascinating speculations about the role of malnutrition in general, and of protein malnutrition specifically, in the ætiology of some diseases prevalent in the tropical regions.

In the strictly temperate Mediterranean-type climate of Cape Town interracial studies have been pursued in freedom from the complicating effects of tropical disease which make interpretations of the role of malnutrition difficult throughout a large part of the Central African belt.

Of the two non-white racial groups, one—the Cape coloured people—has followed for more than a hundred years the cultural and dietetic pattern of the European, and differs in no radical sense from the equivalent pattern of the underprivileged European.³⁸ The other group—the Bantu—comes from a rural pastoral background in which the cultural and dietetic pattern is vastly different from that of the European. Very few of the Bantu have been urbanized for more than a generation, and the great majority are migrant

labourers returning to their homes after living for a year or two in the city.⁴⁸ These migrant labourers retain to a very large extent the cultural and dietetic background of their home environment, while their urbanized brethren—a small minority—are slowly trending towards the European pattern. During his brief stay in the city environment the Bantu migrant labourer tends to produce, even in the year 1960, florid scurvy, the very disease which led the Dutch East Indies Company in 1652 to establish a revictualling station for their commercial navy on the site which has now become the City of Cape Town.¹⁸⁵

The contrast between White, Cape Coloured and Bantu experience of ischaemic heart disease led to studies on the role of quantity and quality of dietary fat in the aetiology of this important degenerative disease of privileged westernized people which have been recorded in a symposium on dietary fat, cholesterol metabolism and coronary disease.³⁸⁹ This fascinating field of study has also been reviewed in Chs. 8 and 19. In the symposium a review on ischaemic heart disease in African populations⁵³ has covered the background of the various racial groups in the African continent. Their mode of life and particularly their dietary habits have been recorded in a chapter entitled *Interracial studies in the South Western tip of the African Continent in relation specially to Cirrhosis and Primary Cancer of the Liver*.⁹⁴ The subject of endemic cirrhosis and primary cancer of the liver in the Central African belt and some other parts of the world is reviewed in Ch. 13. Its relevance to this book is in the theory that chronic protein malnutrition sensitizes the liver to the action of cirrhotogens and carcinogens which could be resisted or detoxified by a well-nourished system.

Nutrition Literature. Apart from the two text books^{91, 447} referred to in the preface there are many general and special texts that can be consulted. On the American scene the first edition of Jolliffe's "Clinical Nutrition" is now slightly out-of-date, but a second edition is due in 1960 or 1961. For a compact reference to facts on applied biochemistry and physiology of human nutrition the "Heinz Handbook of Nutrition" (1959) is invaluable.

This monograph emphasizes the importance of malnutrition in the tropics and in the aetiology of some "tropical diseases". Comprehensive literature in this field is less satisfactory and up-to-date. Two recent books constitute, however, valuable background reference to the important interrelationships between nutrition and parasitic disease in tropical paediatrics; "Infant Nutrition in the Sub-Tropics and Tropics", by D. B. Jelliffe,²¹² and "Diseases of

Children in the Sub-Tropics and Tropics", by H. C. Trowell and D. B. Jelliffe.⁴⁰⁸

The journals now devoted to nutrition, even if one limits one's interest to clinical application, are almost too prolific for review. In the English language the author would like to pay tribute to the value of *Nutrition Reviews*. The short reviews in this admirable journal are critical, topical, timely and most helpful. For abstracts in all fields *Nutrition Abstracts and Reviews* is still pre-eminent. Other international reviews are published in *Excerpta Medica* (Amsterdam).

It is difficult to recommend nutrition periodicals to the general physician who will probably refer to them only as he is led by one of the reviews or abstracts. In the English language the Nutrition Society of Great Britain publishes regularly the *British Journal of Nutrition* and the *Proceedings of the Nutrition Society*. In the U.S.A. the *American Journal of Clinical Nutrition* and *Metabolism*, both contain nutrition articles of general interest to the physician. The *Journal of Nutrition*, official organ of the Institute of Nutrition of the U.S.A., is less clinically oriented.

Tropical journals such as the *Transactions of the Royal Society of Tropical Medicine and Hygiene* and the *Journal of Tropical Nutrition* often contain important articles on clinical nutrition and the same is true of many general medical periodicals such as the *Lancet* and the *American Journal of Medicine*. Very recent nutrition communications in the U.S.A. are picked up quickly in *Federation Proceedings*.

1959 saw the birth of *World Review of Nutrition and Dietetics* under the editorship of G. H. Bourne.³³

In the 1960 volume of *Annual Reviews of Medicine* there is a chapter on *Nutrition and Nutritional Diseases*, by N. Jolliffe and R. S. Goodhart.²¹⁹

CHAPTER 2

FOODS, CALORIES AND NUTRIENTS

THE term *foodstuff* is defined as "anything which can be used as food". In the plural it can be abbreviated to *foods*. (By contrast the word food (nutriment) is often used to indicate a mixture of foodstuffs which appeals to taste and satisfies hunger.) Foods are used to yield energy and to build up and repair the body. Energy is obtained by breakdown of food through various pathways, but especially through oxidation of acetyl coenzyme A, the common channel into which carbohydrates, fats and many proteins go via 2-carbon acetate fragments before ultimate oxidation. No clear distinction is ordinarily made between *foods* and *nutrients* and this sometimes leads to confusion since foods are variable combinations of nutrients. Thus, in the BMA recommended allowances⁹⁰ proteins are listed as nutrients although they consist of a variable pattern of amino-acids which, at least in the case of the essential amino-acids, are their ultimate nutrients. Furthermore almost all foods contain some protein and what are correctly called protein-rich foods (often wrongly called proteins) consist of proteins (with a variable pattern of amino-acids), carbohydrates, fats, vitamins and minerals—not to mention water. In Ch. 7 this subject is further developed in relation to the confusion which has arisen over the term *protein malnutrition* which is far from synonymous with either *protein deficiency* or *amino-acid deficiency*. Similar principles can be applied to the consideration of fatty foods, fats and fatty acids and to starchy foods, carbohydrates and the various sugars which make up carbohydrates, it is doubtful whether knowledge is ripe for a clear distinction between the terms *foods* and *nutrients*, but the ambiguity of present terminology should be appreciated.

Carbohydrates, fats and proteins are to some extent interchangeable as sources of energy, but their cost is very different. Carbohydrate foods are the cheapest for yielding energy and provide up to 90 per cent of the energy needs of poor people, especially in the tropics. In the diets of the rich this figure may be less than 50 per cent and proteins become a considerable, and expensive, source of energy. It is suggested that 55 to 65 per cent is an optimum

and economic figure,⁹⁰ but higher figures may still be consistent with optimum health and may become necessary if population pressure increases.

In urban civilization foodstuffs may be fresh or preserved, natural or processed. Natural foodstuffs may contain poisons, (e.g. senecio, causing bread poisoning), pesticides (arsenic, parathion), or pathogenic micro-organisms (*salmonellæ*, *brucellæ*, *Mycobacterium tuberculosis*). Foodstuffs may become contaminated during distribution (*streptococci*, *staphylococci*). They may become poisoned by preservatives (boric acid) or lose nutrients by spoilage (vitamin C). Processed foodstuffs may lose nutrients in the course of processing (vitamin B₁ in white bread) or be altered in chemical form (hydrogenation of oils). Losses of nutrients during processing may be made good by industry and commerce with or without legislation (synthetic thiamine in white rice and white bread). Foodstuffs may also be used as vehicles for enrichment or fortification with nutrients which may be deficient in the total diet (e.g. the incorporation of milk powder or soy-bean flour in bread).

The importance of quantity and quality of protein in foods is discussed in Ch. 7 with special reference to the concept of protein malnutrition and its short- and long-term effects. The concept of relating protein quantity and quality to calorie intakes is illustrated in Figs. 2 and 3 in Ch. 7.

Dietary fat was, until the decade under review, thought of as a concentrated and palatable source of calories and as a vehicle for the fat-soluble vitamins. Studies initiated during the last decade have shown how much more complex the subject is. Dietary fats are compounds of complex lipids and even the triglycerides vary greatly in respect of the degree of saturation, the chain length and the state of isomerization of their constituent fatty acids. These variations have proved to have the greatest significance in relation to human health. It now appears that just as there are essential amino-acids in protein foods which the human body cannot synthesize so there are essential fatty acids (E.F.A.) which must be supplied in the diet.

In Ch. 9 it is briefly pointed out that the complexity of starches and carbohydrates must be analysed in the coming decade in much the same way as the proteins and fats have been analysed in the last decade. In the same chapter the nutritional significance of trace elements as essential nutrients is stressed. The better-known field of vitamins is briefly reviewed.

Water and Electrolytes as Nutrients

From the point of view of the clinician water and minerals, with the exception of calcium and iron, are not ordinarily thought of as nutrients because they appear to be provided adequately even by the poorest diets. Clinicians realize, however, the ease with which deficiency is conditioned by abnormal losses through vomiting, diarrhoea, sweating and loss of blood or plasma; under these circumstances "normal" intakes rapidly become "inadequate".

Under temporary conditions of water shortage, the body has power to conserve its resources, chiefly by restricting water elimination through the kidneys. Elimination of water through the skin and lungs is largely determined by ambient temperature and humidity and at high-dry temperatures irreducible water losses are very substantial through these routes even with minimal body activity. An impending shortage is rapidly complicated by any unusual water losses as from diarrhoea, vomiting, and loss of blood or plasma. Apart from oxygen, therefore, water is the nutrient, deprivation of which, can most readily produce serious disturbance of homeostasis. Loss of water by all the routes mentioned, with the exception of the lungs, is accompanied by loss of electrolytes. Reserves of these in the body vary greatly. The kidney also has varying capacities to conserve different electrolytes by cutting down their excretion to an irreducible minimum. The irreducible minimum is, for example, considerably greater for potassium than for sodium. The body's reserves also vary greatly for different electrolytes—for calcium the reserve level is very high. The labile pool also varies greatly—for example the extracellular sodium pool is probably temporarily much more dispensable than the intracellular potassium pool. For the cations sodium, potassium, magnesium, and the anions chloride, carbonate and sulphate the body probably has very little reserve or manoeuvrability in the face of low intakes. Progress in the correction of these *conditioned* deficiencies has been very rapid in the last decade. Two contributions have been invited for this monograph to cover, for the adult and the child respectively, these and other important aspects of the relationship of oedema and malnutrition (Ch. 20). The problems at different ages are similar in principle but different in practice because of the greater ease of serious fluid loss in infants through vomiting, diarrhoea and even sweating.

CHAPTER 3

THE RELATION OF NUTRITION TO FEEDING

APART from various types of parenteral feeding used by the medical profession under special circumstances, the provision of nutrients to the body is ordinarily achieved by the consumption of foodstuffs, their digestion in the upper gastro-intestinal tract, and their absorption or assimilation into the blood stream directly or indirectly via the thoracic duct. From that point they are taken over by the body for metabolism and excretion.

The consumption of foodstuffs and nutrients is a basic necessity of life. It is ordinarily achieved by the combined stimuli of hunger and appetite. Both depend upon a complex mixture of somatic and psychic ingredients, but for practical purposes hunger is mainly somatically determined and appetite mainly psychically determined. The potential dominance of the psychic factors controlling appetite over the somatic urge of hunger is illustrated by the disease *anorexia nervosa* occurring in a patient living in a privileged home. Its vagaries at all ages, but particularly in young children, are well known to all medical practitioners and especially to pædiatricians. The child seems to be able to use the control of appetite as a means of achieving control over its parents and nurses.

On the other hand the potential dominance of the somatic functions of hunger over the psychic factors of appetite is illustrated by many examples from the history of famine and of starvation induced by the neglect or brutalities of man. The insistent somatic and psychic urge towards survival in severe hunger and starvation may completely overcome all the finer instincts of unselfishness and lead to the personal acquisition and consumption of anything which might yield calories or nutrients no matter how disgusting the process might be to the ordinary appetite of that individual under better circumstances. The effects of under-nutrition on man's psychic and emotional state are well documented in Keys' "*Human Starvation*".²³⁵

Once foodstuffs have been masticated and swallowed they enter what might figuratively be described as the lumen of a hollow tube which ends at the anus. Under the influence of a variety of factors,

metabolic, infective, physical, chemical, and even malnutrition, foodstuffs may be hurried through the tract to its lower end before the processes of digestion and assimilation can be properly carried out. Under other circumstances foods which have entered the stomach may be vomited or regurgitated. Both psychic and malnutritional factors may contribute to this loss of foodstuffs. The deficiencies and disorders of the processes of digestion and assimilation have been discussed with particular reference to those which are themselves the result of malnutrition and which set up a vicious circle between diet and gastro-intestinal function (Ch. 3).

Once the nutrients have reached the bloodstream in proper order and combination they are available for the processes of metabolism upon which the achievement of good nutrition depend. These processes depend upon a great number of factors and can be adversely influenced by almost every disease described in a text book of medicine. Even psychic factors may impair metabolism. Finally the waste products of the diet must be eliminated through the kidneys, the colon and perhaps other parts of the intestinal tract, the lungs or the skin. Failure in any of these processes of elimination will impair metabolism and nutrition. Vicious circle mechanisms between diet and metabolism and between diet and excretion are described in Ch. 3. It is evident therefore that the eating of a proper diet or a proper combination of nutrients is the first essential but by no means the only factor controlling nutrition.

As a working definition of the term "human nutrition", the simple phrase "those aspects of structure and function which are particularly dependent on proper feeding" is put forward as useful to the physician. This is only a relative definition since in the last resort all structure and function are dependent upon proper feeding, and "optimum health" becomes dependent upon "optimum feeding". The terms health and nutrition are not, however, coterminous, the former, although it depends on the latter, depends at the same time on many other factors.⁴⁶

For practical convenience it is customary to divide malnutrition into two broad groups, (1) dietary malnutrition; and (2) conditioned malnutrition.

Dietary Malnutrition. This can be defined as malnutrition resulting from failure to consume the right combination of food and nutrients to meet the requirements of growth, repair and energy expenditure existent at that time for the individual. The quantity of nutrients laid down in various *recommended allowances* should be sufficient to meet these requirements except under exceptional conditions of

stress, since these recommended allowances usually allow a considerable margin ($33\frac{1}{3}$ to 50 per cent) above the assessed minimum requirement for basal conditions. These same recommended allowances if consumed regularly by a person under basal conditions in a protected environment are not likely to be excessive except in the case of calories. The requirement of the latter has therefore been laid down in exact terms in relation to a variety of activities and stresses (Ch. 11).

Conditioned Malnutrition. Once the food or nutrients have entered the upper end of the lumen of the intestinal tube their availability to the welfare of the individual may be conditioned by a variety of hazards so that, for that individual at that time, they become inadequate. Conditioned malnutrition is usually discussed in relation to disorders of digestion and absorption or assimilation. The principle applies also, however, to conditioning through disorders of metabolism and excretion. Any disease or disorder associated with fever, toxæmia or other constitutional disturbance may increase the requirement for one or more or all nutrients above normal. The importance of loss of iron from sweat and the shedding of epithelium under conditions of heavy work in tropical climates has been emphasized in Ch. 32. Losses of nitrogen in sweat constitute an important unmeasurable variable in the interpretation of information about protein metabolism derived from nitrogen balance experiments..

The Vicious Circle of Dietary Malnutrition with the Functions of Digestion, Assimilation, Metabolism and Excretion. In the discussion in Ch. 4 it becomes clear that malnutrition may affect any tissue of the body with resultant disturbance in function and later in structure. At all stages and in all varieties of malnutrition these disturbances of function may in turn condition a further state of deficiency. This inter-action may constitute a vicious circle mechanism in which malnutrition raises dietary requirement for one or many nutrients.

Such vicious circle mechanisms may operate at three main levels:

- (1) The functions of digestion and assimilation (gastro-intestinal tract mainly).
- (2) Metabolism (anabolism and catabolism).
- (3) Excretion (including kidney, gastro-intestinal tract, skin and lung).

Of the three, the first is by far the most important and (2) and (3) will only be briefly dealt with before going on to the vicious circle mechanism in relation to the gastro-intestinal tract, metabolism

and excretion. Metabolism is used here in a wide sense to include those chemical and enzymic processes which are controlled by many factors including psychic and endocrinal.

An example of a vicious circle mechanism with metabolism is the fatty infiltration of the liver seen in kwashiorkor and which we know to be reversible by dietary treatment. The functions of the liver must presumably be adversely affected by so serious a structural change although we do not know much about these effects. We know at least that many enzymes are depleted in liver biopsy samples.⁴³² The abnormal glucose tolerance test results in kwashiorkor²³⁶ constitute further evidence.

The control exercised over metabolism and homeostasis by the endocrine glands provides an obvious role for a vicious circle mechanism. This is referred to in Ch. 27. An example of a vicious circle mechanism with excretion is to be found in the albuminuria and increased amino-aciduria of kwashiorkor and of potassium deficiency.⁸⁹ These again are reversed by dietary therapy. While they exist they must contribute to the overall deficiency of protein and amino-acids.

One result of the effects of dietary malnutrition on the functions and structure of the gastro-intestinal tract is to initiate a vicious circle mechanism whereby deficiency of nutrients in the diet is aggravated by resultant failure of the gastro-intestinal tract to pass these nutrients successfully into the blood and lymph and so into the processes of metabolism. This vicious circle mechanism is of the utmost importance in practical human nutrition.

A short summary of recent views on gastro-intestinal digestion and assimilation is necessary here prior to consideration of the effects of dietary malnutrition on these functions. It will be shown that the gastro-intestinal tract is very sensitive to dietary malnutrition with resultant impairment of these functions. The clearly recognizable results are disturbances of motility and secretion, of absorption and finally of the pattern and functions of the bacterial flora which both synthesize nutrients and compete for them with the host. Malnutrition often expresses itself through disturbances of tone, motility and secretion which impair appetite and digestion and provoke diarrhoea.

The Physiology of Intestinal Absorption. Intestinal absorption may be defined as the sum of the complex processes by which nutrients pass from the lumen of the intestine through the mucous membrane into the circulation of blood and lymph.

The study of diffusion of soluble ions across an inert membrane

such as cellophane can be used to study some of the factors which influence gastro-intestinal assimilation. It can be shown for example that excess of an ion such as Fe can lead to precipitation of phosphorus as an insoluble phosphate and thus lead to interference with assimilation of phosphorus in the diet.⁵⁶ The inference obtained from this model was applied to the living animal by inclusion in the diet of excess iron with the production of phosphorus-deficiency rickets in rats.⁵² This effect could be neutralized by addition to the diet of further phosphorus sufficient theoretically to precipitate all the excess iron. Complementary studies by mineral balance on humans confirmed that excess iron in the diet can impair the absorption of phosphorus, presumably also by precipitation of insoluble phosphates.³⁷

Interference with the assimilation of a variety of ions by insoluble salt reactions had previously been demonstrated, e.g. high-calcium low-phosphorus rickets (Steenbock), etc.^{34, 52} Many examples of interference with the absorption of organic nutrients by excess of another nutrient in the diet have been recorded since that time. It has frequently been claimed that mineral oils such as paraffin used as a laxative may impair the absorption of nutrients and lead to malnutrition.⁸² Fats appear to interfere with the digestion and absorption of starches in steatorrhoea. Evidence for competition between amino-acids for the absorptive mechanisms has been discussed under the heading of amino-acid imbalance.²⁰²

However, it became apparent long ago that processes of absorption and assimilation were far more complex than might be suggested by the cellophane model. Pioneer work by Verzar⁴²⁰ showed that the absorption of so simple a substance as glucose was dependent upon phosphorylation processes in the intestinal wall which in turn were under the control of the adrenal cortex. Much work has accumulated since then to demonstrate or suggest that almost every nutrient is absorbed by processes which lead to the expenditure of energy by the intestinal cells.

In a symposium on absorption mechanisms and the malabsorption syndrome³⁸⁵ these processes are reviewed in respect of amino-acids, sugars and the ingestion of particulate matter by cells with accompanying expenditure of metabolic energy on the part of the cell. The theoretical possibility is therefore obvious that dietary malnutrition might interfere with this energy-expendending metabolism on the part of the intestinal cells with resultant interference in the dynamic processes of absorption and assimilation.

The inhibitory or interfering effect of trimethylhexadecyl-

ammonium stearate on the same vital processes is mentioned here as evidence of the vulnerability of these dynamic processes.

Results of Malnutrition on Digestion and Absorption. The patterns of the effects of malnutrition observed in the colour and texture of the tongue have long been studied at the bedside²²⁰ and it has been reasonably assumed that these pathological appearances might have their counterpart in the remainder of the gastro-intestinal tract. The raw beef tongue of pellagra is well known and it is reasonably inferred that the diarrhoea is an expression of similar structural changes in the intestine. In recent years, inspection of the gastric mucosa by gastroscopy and biopsy of the intestinal mucosa by intestinal intubation have confirmed these impressions.⁴⁵⁴

Attention was first drawn to disturbances of the level of digestive enzymes in the duodenum in protein malnutrition by Veghelyi⁴¹⁹ who recorded the restoration of secretion by milk feeding. Many other workers since then have shown the same thing in kwashiorkor resulting from protein malnutrition.^{151, 400}

The subject of nutritional effects on the metabolism of the gastro-intestinal tract has been reviewed recently by Vitale *et al.*⁴²¹ Their review is concerned mainly with experimental pathology in animals, but in a final brief paragraph they mention some clinical aspects. There can be no doubt at all about the experimental basis for postulating a vicious circle mechanism between dietary malnutrition and the processes of intestinal digestion and absorption. The expression of this vicious circle in man has yet to be adequately explored and established.

Platt³²⁰ has recently reviewed the demonstrated and possible effects of dietary malnutrition on gastro-intestinal function in the infant. He starts with the statement that veterinary nutritionists know that the runt has, compared with its litter mates, impaired digestion. This deficiency must undoubtedly complicate the problem of digesting the relatively small amount of food which the runt is able to get in competition with its larger litter mates and must further a vicious circle of nutrient deficiency initiated by the unfavourable birth size and strength. Werner's⁴³⁸ evidence is then quoted showing that the premature infant is not so well endowed as is the normal infant with pepsinogen granules in the gastric mucosa or with zymogen granules in the pancreas. A similar vicious circle must develop here, the premature infant having to contend with weakness of sucking even if it is free from the competition of litter mates.

Platt then suggests that the immature (although not premature)

infant born of a mother suffering from protein malnutrition may have similar gastro-intestinal defects which again may produce a vicious circle. This latter mechanism is not very likely to be important in the aetiology of kwashiorkor since available evidence indicates that these infants usually obtain normal quantities of breast milk and grow normally up to the time when they are "deposed" from the breast by the succeeding sib. But it may well be an important mechanism in the causation of marasmus and infantile diarrhoea. Platt's own studies on the comparative effects on the histology of the gastro-intestinal tract in piglets submitted respectively to low protein and low-protein plus added carbohydrate diets may well help to clear up the present obscurity in the pathogenesis of marasmus and kwashiorkor.¹⁷⁸ His group has confirmed³²⁰ by tritium studies the long suspected high rate of protein turnover of the gastro-intestinal cells and provided a sound basis for the concept that this system is likely to suffer early and severely in developing protein malnutrition, so aggravating dietary deficiency through a vicious circle mechanism.

Intestinal Bacterial Flora. Since the early work on refection¹³⁶ it has been recognized that certain commensal micro-organisms of the gastro-intestinal tract may be capable of synthesizing vitamins required by their host. In the case of certain vitamins (vitamin K and certain members of the B group) this may represent a quite considerable contribution to the nutrient economy of the host, particularly when dietary intake of the vitamins concerned is low or marginal. An obvious corollary of this function of the intestinal bacterial flora is that they may, by competition, deprive their host of ingested vitamins and other nutrients. Attempts have been made to put both directions of this two-way traffic on a quantitative basis through the study of germ-free animals. Because of the potential importance of this new line of enquiry a chapter has been included in this book (Ch. 22).

The introduction of the broad spectrum antibiotics and their use in man has emphasized another important aspect of intestinal bacterial symbiosis, probably independent of the effect of the bacteria on vitamins. The disastrous staphylococcal enteritis which sometimes follows the use of broad spectrum antibiotics, and the less dramatic but important monilial invasion which may also result, illustrate the value of intestinal commensal micro-organisms in protecting the intestinal tract against invasion by pathogens. Judging by the serious effects of staphylococcal and monilial invasion this protective effect must indeed be important to man. In

a very real sense he lives in a state of symbiosis with his intestinal bacterial flora.

By analogy with herbivorous animals it might be expected that even in omnivorous man the composition of the diet might well affect the pattern of intestinal bacterial flora. In Ch. 22 György describes the differing effects of human and cow's milk on this same pattern. In Ch. 29 Scrimshaw refers to the important inter-relationships between malnutrition and pathogenic bacteria in the ætiology of kwashiorkor. In Chs. 7 and 23 references are made to the role of changes in commensal bacterial flora in the ætiology of kwashiorkor and infantile gastro-enteritis as discussed by Smythe.³⁷¹ The importance of change in the antigenic strain of *E. coli* prevailing in the colon in determining epidemics of neonatal diarrhoea is well established.

The effect of penicillin on megaloblastic anæmias is also interesting. The macrocytic anæmias with megaloblastic hyperplasia of the bone marrow are far more common in tropical than in temperate climates. One feature of the life of poor people in the tropics is their great dependence upon vegetable protein which may lead to deficiency of vitamin B₁₂. Foy and Kondi¹³² have produced evidence that this type of anæmia can be improved by penicillin both by the oral and parenteral route. They believe that the penicillin, in altering the intestinal flora, removes bacteria which compete for vitamin B₁₂, or which inhibit other bacteria that synthesize vitamin B₁₂ (see Chs. 13 and 32).

Another point of great public health significance is the vicious circle mechanism between malnutrition, gastro-intestinal flora, and diarrhoea. Summer diarrhoea is one of the important causes of death among infants in underprivileged communities. Culture of the stools often reveals no pathogenic organism.²²⁵ It is more than possible that this form of diarrhoea is itself the result of impairment of normal symbiotic relationships in the digestive tract as a result of malnutrition. The subject has been recently reviewed in relation to local infants.³³⁰ This review demonstrates clearly the relationship of malnutrition to gastro-enteritis. The view is expressed that "it is in the main the child that is already suffering from malnutrition who becomes a victim, and a vicious circle is frequently set up, worse malnutrition following each repeated attack of gastro-enteritis, leading finally to kwashiorkor or death". This problem is also dealt with in Chs. 23 and 29.

Having reviewed briefly the physiology of digestion, and the effects of malnutrition on gastro-intestinal function and the bacterial

flora of the intestine, it can be indicated in summary that a great variety of forms of malnutrition acting through a variety of gastrointestinal mechanisms can impair the normal physiology of digestion and assimilation in such a way that a further deficiency is conditioned and a vicious circle mechanism is set up. This vicious circle is well exemplified in a recent discussion of the relationship between achlorhydria and anaemia.¹²⁰ If iron deficiency is both a cause and a result of achlorhydria then we have a beautiful example of a vicious circle. A similar type of vicious circle may be operative in relationships between folic acid deficiency and secretion of intrinsic factor. Few would deny the possibility that there is probably a genetic defect in many of these cases but, in terms of the discussion of malnutrition and constitution in Ch. 14 it is very likely that malnutrition is one of the environmental factors which precipitate breakdown in a genetically unstable system.

CHAPTER 4

RESULTS OF DEFICIENCY OF NUTRIENTS

WHETHER the nutrients which reach the blood stream for the processes of metabolism are deficient in quantity or balance and whether the deficiency is due to defective diet or is conditioned by disorder of the gastro-intestinal tract, there will be consequential results upon every vital process, and therefore ultimately upon every organ and tissue. These disturbances will in the first place affect function, chemistry and metabolism, but later they will result in disturbances of structure.

Clinical classification of the results of dietary malnutrition is difficult, but after teaching clinical nutrition to medical students for 22 years, I have found it convenient to divide these results under four headings:

- (1) sub-nutrition (sub-clinical malnutrition);
- (2) reversible clinical syndromes of malnutrition;
- (3) irreversible structural damage;
- (4) constitutional susceptibility (diathesis) from chronic malnutrition.

It is possible that the first and second headings cover most of the manifestations of acute or short-term malnutrition. Chronic or long-term malnutrition needs to be considered under all four headings. Although it is the mildest degree, sub-nutrition is discussed after the concepts of two of the more severe degrees have been clarified.

Reversible Clinical Syndromes of Malnutrition. In these syndromes the disturbance resulting from deficiency in quality or quantity of nutrients provided to the blood stream is in the first place biochemical or metabolic and results in disturbance of function. When the malnutrition is simple, i.e. uncomplicated, and due to deficiency of a single nutrient, and has not been too prolonged, the disturbance can apparently be completely reversed within minutes. This situation is exemplified in experimental physiology by the student class example of the thiamine-deficient pigeon in a state of head retraction and paralysis which is walking or flying within a few minutes of an injection of thiamine.⁹¹ In clinical practice it is also exemplified by

the results of intravenous infusion of glucose in a hypoglycæmic subject. If the deficiency is simple, but has been prolonged, considerable time may be required before the beneficial results of supply of the nutrient may be apparent. In iron deficiency states, the supply of iron may be followed by a rise in reticulocytes occurring between the fourth and tenth day and a rise in hæmoglobin starting about the seventh day. Improvement in appetite and sense of well-being often coincides with the reticulocyte rise.

¹ In latent scurvy, the administration by mouth of a test dose of ascorbic acid 11 mgm./kg./day will yield very little if any increase in urinary secretion of ascorbic acid for 3, 4 or 5 days, whereas the same dose administered to a healthy subject will provide an appreciable rise in urinary ascorbic acid within the first 24 hours.¹⁷² This difference in dose response probably reflects the extent of the stores of ascorbic acid in the body which require to be replenished before any significant excretion of the vitamin occurs through the kidneys. If the ascorbic acid is administered intravenously, there will be immediate spill-over into the urine as the renal threshold for ascorbic acid is exceeded, but saturation can be achieved much more quickly. An acute oral tolerance test as measured by plasma ascorbic acid levels has been recently described.¹¹² Improvement in sense of well-being and improvement in capillary fragility may occur within a few days provided dosage is adequate.⁸⁴

Complex Malnutrition. In the paragraphs above, the term simple malnutrition has been used to indicate uncomplicated deficiency of a single nutrient. In a number of experimental studies, notably that of Crandon, Lund and Dill⁸⁴ on progressive depletion and repletion of humans with ascorbic acid while they were on a diet believed otherwise to be complete, it has been possible to study the effects of such an isolated nutrient deficiency. In ordinary clinical experience, however, malnutrition is almost always multiple or complex, i.e. it results from deficiency of several or many nutrients to varying degrees. This is attributable, of course, to the fact that ordinarily nutrients are supplied as foodstuffs which represent a variable combination of nutrients (Ch. 2). Many errors have been committed in the past and even in the last decade through failure to appreciate this simple principle. Pellagra has, for example, been attributed to niacin deficiency although it is perfectly clear that health cannot be restored by the simple addition of niacin to the diet upon which the patient subsisted while he developed his pellagra. There is almost invariably deficiency of other members of the vitamin B complex, of other vitamins and of total protein. The serum albumin is very

commonly reduced. In the clinical syndrome of pellagra, niacin can be described as the most-limiting nutrient in a complex deficiency state. Provision of niacin alone will reverse temporarily the more severe clinical disturbances such as the fiery red tongue and diarrhoea, but it will not restore health. On the other hand, when populations are subsisting on diets which lead to pellagra, as when the staple cereal and source of calories is maize, addition of niacin to the diet may prevent pellagra in the great majority of the population although it will not produce a healthy population.

Another example of error in this context is demonstrated in the syndrome which we now know as kwashiorkor and which can be cured with skimmed milk or even with a synthetic formula. For many years it was called infantile pellagra. This name was used principally in the maize areas of the world and probably derived from the fact that the infants had a dermatosis which was at least pellagroid if it did not justify the name pellagra. Even this pellagroid rash has been shown to heal, with partial initiation of cure, on a formula of glucose, amino-acids and salts in water without any known vitamins.¹⁶⁹

Reversible Structural Damage. If the state of malnutrition is continued long enough or is severe enough, the biochemical or metabolic disturbance will be followed by structural abnormality which can be recognized either through the microscope or later by naked eye. In vitamin A deficiency, for example, in experimental animals metaplasia of the respiratory epithelium is the first recognizable histological abnormality.⁴⁵⁰ In humans the structural abnormality resulting from ascorbic acid deficiency is seen early in the petechiæ resulting from abnormal capillary permeability and in the spongy gums. This latter classical sign of ascorbic acid deficiency is often absent if the patient is edentulous, suggesting that it is due to the combined effects of vitamin C deficiency and infection. In severe scurvy there may be hæmorrhage in the inter-muscular septa and in or under the periosteum. In the former site, the hæmorrhage often produces a presenting sign of lameness due to painful swelling of the muscles of the calf or thigh. Scurvy usually presents this way in the Bantu of Southern Africa,⁵⁷ although classical literature on scurvy presents a somewhat different picture.^{185, 252}

In the above examples, microscopic and macroscopic structural damage, the sequelæ to chemical or metabolic disturbance, is still completely reversible. In isolated examples, e.g. ascorbic acid, it may be reversible by provision of adequate quantity of a single

nutrient. In the vast majority of cases reversal and restoration to normal health requires the provision of a full diet plus supplements of one or more most-limiting nutrients.

Irreversible Structural Damage. If deficiency which leads to reversible structural damage is continued long enough or in severe enough form, there will be death of tissue. In the central nervous system, such death is irreversible. Thus, for example, deprivation of the brain for 30 minutes or less of either oxygen or glucose will lead to irreversible structural damage which may express itself clinically as permanent neurological defect or dementia. In the peripheral nervous system under the influence of thiamine deficiency neurones may degenerate from the periphery back towards the cell nucleus. Until the cell nucleus has died, the neurone is capable of regeneration when thiamine and a full diet are provided although this process may take 6 months. Once the cell nucleus has died there is no further regeneration of that neurone. This explanation undoubtedly accounts for cases of permanent partial paralysis resulting from alcoholic and other nutritional polyneuropathy.

The same principles apply to other structures, although outside of the central nervous system the body has a much greater capacity for replacing necrotic cells. In many tissues this capacity is so full of potentiality that gross degrees of structural degeneration resulting from malnutrition may be apparently completely repaired. This is certainly true of mucous membranes and skin in which apparently complete structural normality can be restored after widespread nutritional damage.

It is very interesting to speculate about the possibility of irreversible myocardial damage from chronic malnutrition. Mention has been made (Ch. 13) of prompt improvement in function and less prompt reversion of the electrocardiograph to normal in thiamine deficiency heart disease. Similar reversibility has been shown for alcoholic cardiopathy by Evans.¹²² In the group of cases of chronic unexplained cardiac degeneration collectively referred to as cardiopathy of uncertain origin (Ch. 30) we are undoubtedly dealing with what in most cases is an irreversible cardiac structural damage. The ætiology is still unknown and it is quite possible that several different ætiological groups are at present included under the same terms.

The concept that the myocardial degeneration is the result of malnutrition is hypothetical. This subject is discussed in Ch. 13 on the heart and in Ch. 7 on the ætiology of a variety of disorders which are widely prevalent in underdeveloped nations while rare or

uncommon in developed nations. At the best, the role of malnutrition can only be contributory, but it may nevertheless be a decisive contributory factor in that the exciting agent, whether virus or other infection, endogenous or exogenous poison, might be incapable of producing irreversible damage in a normally nourished tissue. The subject is also discussed in Ch. 13, in relation to the possible malnutritional basis of the widespread liver cirrhosis which in Africa and other parts of the underdeveloped world leads to a high prevalence of primary carcinoma of the liver.

Sub-nutrition (Sub-clinical Malnutrition). There must be a stage of malnutrition short of that which produces a recognizable clinical syndrome resulting from biochemical or metabolic dysfunction, much less structural damage. Identification of such sub-nutrition can, at present, only be indirect and often presumptive. The available methods for its identification are discussed in Ch. 5 under the heading *Recognition and Identification of Sub-nutrition*. These methods fall into two broad groups: (1) demonstration by biochemical means that the tissues of the body generally contain less of a given nutrient than is judged to be optimum for basic requirement or for meeting unusual stresses. This demonstration usually depends upon measuring the excretion of the nutrient in the urine, its level in the plasma, or the effect of loading doses on the plasma level or the urinary excretion. In other cases they depend upon the identification and measurement of a metabolite in the blood or urine which is known to be representative of perverted metabolism and which is reproducible experimentally by inducing deficiency of a specific nutrient. Examples are: the serum level of pyruvic acid in thiamine deficiency and the excretion of N-methyl nicotinamide in niacin deficiency. (2) The second broad group of measures for detection include: the comparison of community statistics for weight, stature, life expectation and morbidity between populations known to be eating diets containing the recommended allowances of nutrients with similar statistics of populations known to be consuming diets inadequate by the same standards. Unfortunately, the community receiving a deficient diet is almost always unfavourably situated in comparison with the control population in respect also of hygiene, housing, clothing, education and often tropical parasites and tropical climates. It is therefore impossible to assess the extent to which malnutrition is contributory. Improvement in the diet is often the simplest corrective to achieve and the results of doing this alone without correcting other defects in the environment may constitute presumptive evidence of the role of mal-

nutrition in ætiology. Thus, for example, the universal distribution of a supplement containing a cheap source of calories, some skimmed milk and a vitamin capsule over a period of a year or more may lead to improvement in morbidity statistics for such diseases as pulmonary tuberculosis, infantile gastro-enteritis, diarrhœa and bronchopneumonia. In that case then the deduction can reasonably be made that malnutrition has been in part responsible for the high prevalence of these diseases in the community. Unfortunately, such experiments are difficult to carry out in a controlled manner. They are discussed more fully by Scrimshaw in Ch. 29 on Nutrition and Infection.

Constitutional Susceptibility to Disease (Diathesis) Resulting from Chronic Malnutrition. An adequate understanding is necessary of the way in which habitual diet may determine in part the development of constitution in the individual since such an understanding underlies an approach to the consideration of some diseases of multiple and uncertain ætiology developing in middle life. This group of diseases includes such important degenerative diseases as atherosclerosis, cancer and hypertension. At earlier ages it may include such disorders as allergy, anaphylaxis and the rheumatic, rheumatoid and collagen disorders. This claim is not lightly made. All will agree that the diseases mentioned are of uncertain and probably multiple ætiology and that they have their roots both in the genetic make-up of the individual and in the long-term effects of environmental stresses. Among these stresses we must surely include dietary malnutrition, using the term in its broadest sense to include deficiency, excess or imbalance of nutrients in a great variety of combinations; at least this can be treated as a reasonable hypothesis for further investigation. Two examples, from the work of the last decade, which have profitably used this hypothesis as a basis for investigation are the consideration of (1) the role of quantity and quality of dietary fat in the ætiology of ischæmic heart disease; and (2) the role of protein malnutrition in the ætiology of primary carcinoma of the liver.

Constitution. Fig. 1 illustrates the long-term interactions between genotype and environment in the production of constitution. It was first published in 1948³⁸ after use for 10 years in systematic lectures to medical students on systematic medicine. It was republished in Cluver's "Social Medicine".⁷² It was again republished in 1959⁴⁶ where it is expounded under the heading *Nature and Nurture in the Ætiology of Human Disease*. The concept of constitution built around Fig. 1 puts in different language rather similar thoughts expressed by Trowell in 1949⁴⁰⁴ under the term "life-flight" and by

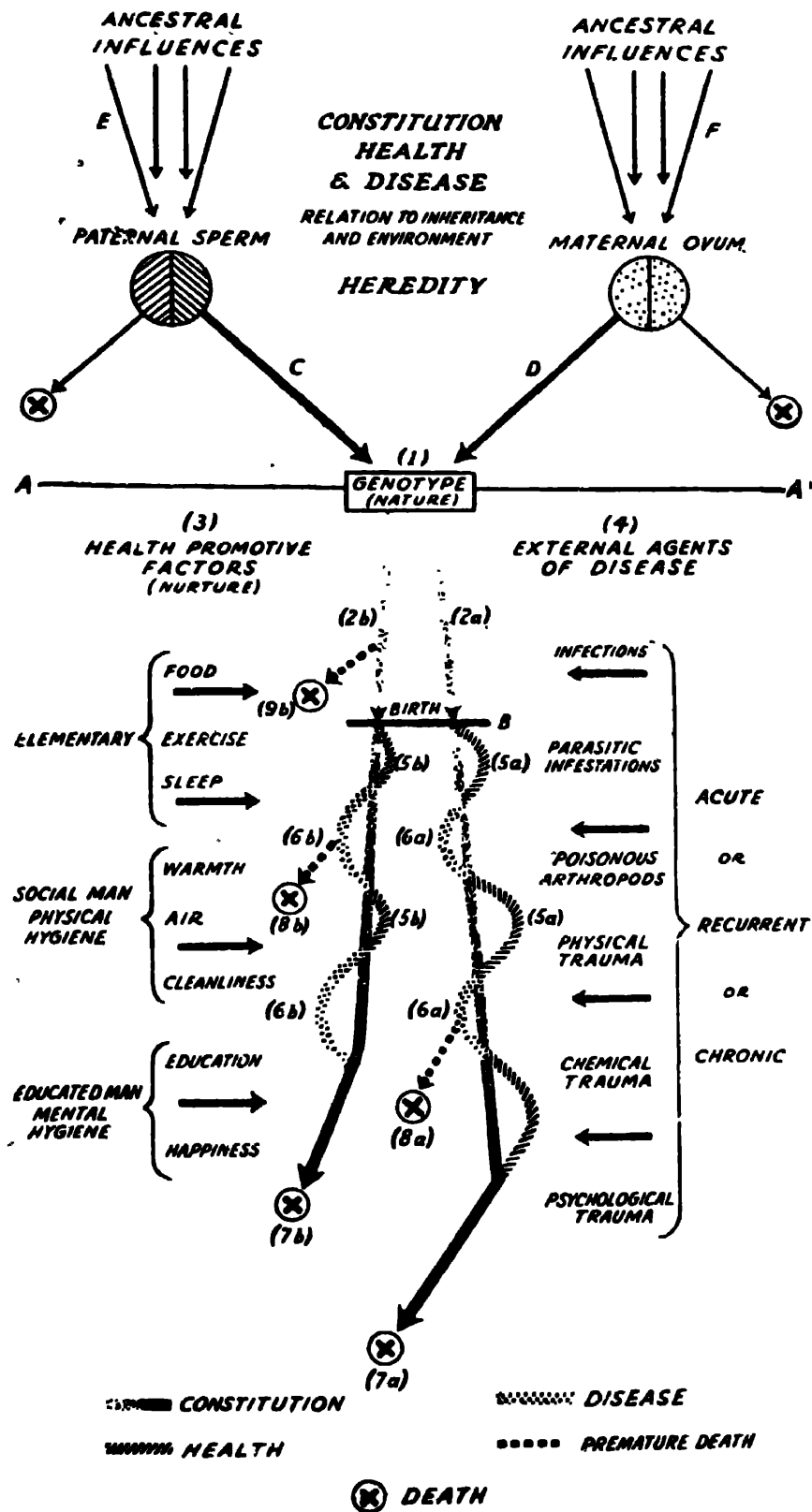


FIG. 1. Diagram illustrating relationships between genotype and environment, both favourable and unfavourable, in determining the development of constitution and life expectation, and of experience of health and disease. The long-term progressive development of a healthy and of an unhealthy constitution are shown in the vertical straight lines; the short-term experiences of health and disease are shown in the sinuous deflections

Gillman and Gillman¹⁴³ in 1951 under the term "life-track". Its understanding is basic to the understanding of principles of clinical medicine in medical practice.

The relevance of this diagram to relationships between diet, health and disease is apparent when we note that the first of the environmental health-promotive factors shown in the left-hand side of the diagram is food. It is described as elementary because it is common to all forms of living organisms and can well be described as the "most-limiting" environmental health-promotive factor since it is the factor deficiency of which will most quickly produce its unfavourable effects on health. In public health and preventive medicine there is no environmental deficiency which can be more readily corrected through the application of existing knowledge.

A healthy constitution is developed by a favourable balance of health-promotive factors over external agents of disease, but is grounded in the genotype. Disease is produced by an unfavourable balance between health-promotive factors and external agents of disease. The latter act more readily on an unhealthy constitution but are capable of causing disease even in a healthy constitution ; ultimately, if their action is severe and prolonged, they may result in the undermining even of a healthy constitution. It is essential to emphasize that constitution is a product of both genotype and environment, a product of nature and nurture. It is never fixed, although its improvement or deterioration are usually achieved only over considerable stretches of time. The short-term fluctuations of health and disease about the slowly evolving line of constitution are represented in Fig. 1. This subject is taken up again in Ch. 14 under the heading *Long-term Cumulative Effects of Malnutrition*.

CHAPTER 5

THE RECOGNITION OF MALNUTRITION AND ASSESSMENT OF NUTRITIONAL STATUS

Reversible Structural Damage

RECAPITULATING the four groups under which the results of deficiency of nutrients were discussed in the preceding chapter: (1) sub-nutrition (sub-clinical malnutrition); (2) reversible clinical syndromes of malnutrition; (3) irreversible structural damage; (4) constitutional susceptibility (diathesis) from chronic malnutrition; it is convenient to start with the recognition of some examples of structural damage which is still reversible. The most easily recognized are those which appear on the surface of the visible mucous membranes and of the skin and its appendages, the hair and nails. Most of these disturbances are reasonably well known, particularly in underdeveloped regions, and are described in many textbooks. Good colour plates are available in the first edition of Jolliffe's "Clinical Nutrition".²²⁰

In the decade under review, however, there have been some important changes in interpretation. Two trends can be recognized:

- (1) the important role of external physical irritants such as heat, cold, wind, dust and salt spray has been given its due recognition which was previously lacking;
- (2) there is less tendency to attribute specific patterns of structural change to deficiency of individual nutrients and more recognition of the mutual interplay of several nutrients. Both these trends are an expression of the growing recognition of the importance of multiple aetiology in disease.

Considering the first of these trends, everyone in cold climates is familiar with chapped lips and in warm sunny climates with bronzing of the skin and bleaching of the hair after long exposure to sunshine and water, particularly salt water. As these changes appear under the influence of the external physical environment in people who are apparently optimally nourished, their relationship to such pathologic entities as cheilosis and achromotrichia is not always recognized. These two pathological entities may result from severe malnutrition in the mildest of climates and with the mildest

of external stresses. On marginal diets greater external stresses will be required to evoke them. These stresses, however, will be milder than those needed to produce the "normal" appearances seen in well-nourished people. In other words, the skin and its appendages are provided to protect man against a harsh environment; in order to do so adequately, they must be properly nourished. High degrees of melanin pigmentation of the skin were presumably evolved as an additional protective measure in very sunny climates; the metabolism of melanin is also dependent upon proper nutrition. The biochemical change in the melanin of hair which, under the influence of protein malnutrition results in dyspigmentation and eventually achromotrichia, has been defined.²⁹² The interactions of the genotype with dietary and non-dietary environmental factors in the production of the dyspigmentation of kwashiorkor were described by Brock and Autret.⁴⁹ Two points of historical interest arising out of this are that it is likely that the only real difference between mehl-nährschaden⁸⁵ and African kwashiorkor derives from the differences in pigmentation between children of Southern Germany and Austria and those of the African tropics. The second is that the term kwashiorkor was thought for some time to refer to the reddish-brown dyspigmentation of the hair of African children with the disease and this false etymology led for some time to failure to recognize the fundamental similarity of the results of protein malnutrition in post-weaning children throughout the world. The newer etymology of kwashiorkor⁵⁰ (Ch. 7) disposed of this confusing factor.

Taking up the second point it is clear that deficiency of a single nutrient seldom occurs in man. It would, therefore, be surprising if structural changes in the mucous membranes and skin specific for riboflavin and niacin were to occur in nature when deficiency of these two vitamins almost always results from a diet deficient not only in the whole of the vitamin B complex, but deficient also in protein. It is surprising how long this simple principle has taken to permeate teaching and textbooks on clinical nutrition. Reference is made in Ch. 7 to a pellagroid dermatosis occurring in children who develop kwashiorkor on maize gruels and other starchy paps and which is curable with a purified formula containing no vitamins at all. Mozaic or crazy-pavement dermatosis of the skin is another non-specific result of malnutrition which has been incorrectly attributed to specific nutrients in the past. The controlled study of its disappearance under treatment with dietary factors is complicated by the fact that almost certainly external trauma and

stresses such as sun and wind play a part in its ætiology, while another part in its cure is often played by enthusiastic nurses applying soap and flannel to a skin which has been innocent of such refinements in the past.

Structural disturbances in internal systems resulting from malnutrition are not easily studied and often depend upon indirect methods. The classical radiological appearances of vitamin D deficiency in the epiphyses of the more rapidly growing long bones is specific for rickets but not necessarily for vitamin D deficiency. It can certainly be produced in animals by disturbing the balance of calcium and phosphorus in the diet, and it is not unlikely that a similar imbalance may be responsible for these changes seen in infants in sunny and tropical climates. This statement is not meant to question the undoubted occurrence of vitamin D deficiency in climates where pigmented children are artificially protected from sunlight.⁴⁰⁶

The effect of kwashiorkor on the growing knee is recorded²²¹ as producing "numerous abnormalities as well as a general appearance of poor calcification". The general effect of malnutrition on the bones of children and of infants *in utero* have been discussed by Platt.³¹⁹ Other structural results of malnutrition are becoming amenable to exact definition by means of new techniques of endoscopy and biopsy, e.g. gastric suction biopsy and liver puncture biopsy. Interpretation of the results of histology is, however, by no means always diagnostic of the nature of suspected malnutrition.

In underdeveloped regions there is a common form of parotid gland enlargement which appears to be the result of chronic malnutrition.^{93, 341} A recent report from French West Africa suggests that lack of adequate protein may be the cause of the parotid enlargement.³²⁶ It is also clear from descriptions of refeeding following periods of starvation, particularly as seen at the end of the Second World War, that the parotid glands may enlarge suddenly with pain.²⁵⁶

In the light of the above remarks it is an interesting illustration of the extent to which medicine and surgery in developed countries is pigeon-holed off from the same subjects in underdeveloped and tropical countries, that a recent symposium on the salivary glands at the Royal Society of Medicine¹⁰³ makes no reference at all to the effects of malnutrition on these glands.

The Earlier Functional Stages of Reversible Clinical Syndromes. Turning back to the disturbances of function which always precede disturbances of structure in the evolution of reversible clinical

syndromes of malnutrition, we are faced with serious difficulties of interpretation. Dietary malnutrition is nearly always complex and several or even many disturbed metabolic processes may coexist. Even if a metabolic disturbance can be traced to a specific dietary deficiency, there often remains difficulty in separating this from similar metabolic disturbances resulting from inherited enzymatic disorders and non-dietary environmental causes. This dilemma has been touched on in part in a discussion in Ch. 3 on the vicious circle mechanism between dietary malnutrition and gastro-intestinal function. It can be further illustrated by examples from other systems.

The problem can be exemplified in the respective effects of thiamine deficiency, oxygen deficiency and glucose deficiency on the nuclei and functions of the central and peripheral nervous system. Central nervous tissue is very rapidly susceptible to disturbance of function from deficiency of oxygen or glucose and indeed death and necrosis may occur within 15 or 20 minutes of complete deprivation. The functional results of the two forms of deficiency are not separable. Thiamine deficiency takes much longer to declare itself, partly because the body carries reserve stores and partly because there are alternative pathways of metabolism which may still preserve function, albeit less efficient.

Attention has been drawn over many years by Walshe⁴²⁵ to the common features of impairment of peripheral neurones, with associated tachycardia, resulting from a great variety of causes of polyneuropathy. It is Walshe's view that many patterns of metabolic disturbance may result in a final common pathway of functional neuronal disturbance. The problem is discussed in regard to the cardiovascular system in Ch. 13 where the transition from reversible to irreversible damage is traced.

It is now generally accepted that identical disturbances of electrocardiographic pattern may result from several different metabolic disturbances having a final common pathway. This can be exemplified in overlapping patterns of departure from the isoelectric axis and RT duration resulting respectively from disturbances in thiamine, potassium and calcium levels in the extracellular and intracellular fluids of the myocardial tissue.

Because of the difficulties described above, the identification of a functional disturbance in any body system as a result of malnutrition will depend on a combination of indirect evidence which will include (a) history of a defective diet; (b) exclusion of non-dietary causes by individual clinical and laboratory examination;

and (c) biochemical identification of sub-normal levels of nutrients or of the presence of abnormal metabolites, e.g. blood pyruvate levels in thiamine deficiency. This aspect of the problem is discussed in Ch. 5. Another desirable criterion is (d) reversal of the functional disturbance by supplying the missing nutrient or nutrients under controlled conditions of experimentation. These controlled conditions are by no means easy to achieve. We have described our experience¹¹⁵ in attempting to define the role of thiamine deficiency in mixed pictures of malnutritional oedema. In brief, when the patient with oedema and suspected thiamine deficiency is brought into hospital, the following errors of interpretation must be avoided:

- (1) the mere confining of the patient to bed as compared with his previous ambulant or working state may result in diuresis and disappearance of oedema;
- (2) the hospital ward diet may supply—in comparison with the patient's previous diet—quantities of thiamine sufficient to restore function during a period of observational control before commencing therapeutic administration of thiamine. There is no doubt in our minds that many examples recorded in the literature of apparent response to therapeutic application of thiamine have remained unconvincing because of lack of attention to these necessary controls.

Sub-nutrition (Sub-clinical Malnutrition). The section just concluded on the recognition of the functional (or non-structural) stages of reversible syndromes of malnutrition merges into a discussion of sub-nutrition. Dietary sub-nutrition can be defined as any impairment of functional efficiency of body systems which can be corrected by better feeding. This definition by therapeutic demonstration is, of course, unsatisfactory, but it would be even less satisfactory to ignore or deny the possibility of its existence. Implicit in the definition is the absence of structural or functional change which can be positively identified as resulting from malnutrition. Its positive identification must depend upon indirect means similar to those which have been described for the earlier or functional stages of reversible clinical syndromes of malnutrition, i.e. definite or presumptive history of defective diet, exclusion of non-dietary causes and biochemical identification. The last of these indirect criteria furnishes the principal hope for scientific measurement in the future. The difficulty for the present is in determining where the border lies between normality and abnormality in these biochemical tests. Some of these quantitative aspects are referred to in the considera-

tion of the results of deficiency of nutrients (Ch. 4). They are more fully dealt with in the I.C.N.N.D. Report *Manual for Nutrition Surveys*⁴¹⁴ discussed below. For the present in the recognition of sub-nutrition the experienced doctor or nutritionist must use the largely subjective and non-measurable criteria of posture, stance, and physical, emotional and intellectual reactivity to test situations. In experienced hands these criteria constitute valuable and sensitive measures of functional efficiency. If disease is excluded and dietary deficiency presumptively established, then improvement in any or all of the criteria as a result of test feeding can carry conviction though it does not constitute final proof.

Assessment of Nutritional Status. This subject was discussed at the first meeting of the Joint FAO/WHO Expert Committee on Nutrition in 1949,²¹⁵ and at its second session the Committee drew up a guide to nutrition workers on this subject.²¹⁶ This is a basic document which should be studied by all who are concerned with the problem. In its fifth report the Committee²¹⁸ recommended the advisability of revising the guide and suggested that it might be studied by appropriate groups of experts. This account of the handling of the subject by international experts over the last decade emphasizes the complexity of the problems involved. Another basic document in this field is *A Manual for Nutrition Surveys* produced by the U.S.A. Interdepartmental Committee on Nutrition for National Defense.⁴¹⁴ This comprehensive manual deals with the sampling of populations, their clinical appraisal for nutritional status, methods of dietary study and details of acceptable methods for biochemical assessment including an interpretative guide. This document will remain a fundamental work of reference for a long time to come.

Special aspects of the recognition of malnutrition as it applies to the recognition of protein deficiency and protein malnutrition are discussed in Ch. 7.

CHAPTER 6

MALABSORPTION SYNDROMES

THIS term has been generally adopted in the last few years to cover a group of disorders affecting the absorptive functions of the gastro-intestinal tract; it includes the steatorrhœas. Some other disturbances of intestinal absorption which are not ordinarily expressed in clinical steatorrhœa will, on chemical study of the stools, show an increased percentage of fat in split or unsplit form. In theory the term includes any form of intestinal malabsorption, whether fat absorption is involved or not. In this sense Addison's pernicious anæmia might be included under the heading because B₁₂ absorption is impaired.

Since the monograph by Adlersberg³ two recent symposia are representative of recent thought in many aspects of this field.^{385, 393}

Although the malabsorption syndromes present some fascinating aspects of secondary or conditioned malnutrition and of a vicious circle mechanism between diet and gastro-intestinal function (Ch. 3), there is comparatively little evidence that any of them are primarily due to dietary malnutrition. They are commonly divided into primary or cryptogenic, and secondary or symptomatic groups. The latter are due to a variety of defined and demonstrable organic lesions of the gastro-intestinal tract from the stomach downwards. In the small intestine steatorrhœa may result from diseases such as lymphosarcoma, amyloidosis, jejunoileitis, strictures and blind loops, or the results of extensive resection of the small bowel, etc.

The primary or cryptogenic group includes coeliac disease in infancy and idiopathic steatorrhœa and tropical sprue in adults. The ætiology of this group is still mysterious, but the age, social grouping and geographical distribution of the first two syndromes mentioned lend little support to dietary deficiency as a direct cause.⁴ Adlersberg describes them as dependent upon genetically-controlled disorders of enzymatic chain reactions. This genetic anlage may become manifest in infancy, in childhood (coeliac disease) or in adult life as tropical or non-tropical sprue. Environmental factors which precipitate recognizable disturbance of the genetically-installed anlage include certainly sensitivity to the gluten of wheat and rye in the diet. The frequency of sprue in

tropical climates suggests, however, that there may be some additional factor, peculiar to tropical climates, which acts as an environmental precipitating agent. At present there is no clue at all as to the nature of this tropical factor. On the one hand Stefanini³⁷⁷ concluded in 1948 that dietary deficiency is an important factor in the development of tropical sprue. On the other hand those who have compared the tropical and non-tropical varieties have been able to distinguish few differences.^{30, 160}

The histological lesion in idiopathic steatorrhoea has been amply documented.³⁶⁶ Its appearance under the electron microscope has been recorded.¹⁷⁶

The detailed morphology is not of interest in the present context except as a background to the observations that when studied by serial jejunal biopsy the atrophy was not reversed by treatment with folic acid, vitamin B₁₂, antibiotics, cortisone or a gluten-free diet.^{68, 366} It would appear, therefore, that the lesions of coeliac disease and of idiopathic steatorrhoea are the cause rather than the result of malnutrition. If the idiopathic or cryptogenic malabsorption steatorrhoeas were due to dietary deficiency, a likely deficiency would be folic acid since it is so effective in the treatment both of the steatorrhoea and of the associated megaloblastic anaemia.³⁷⁷ It would appear, however, that the demonstrated deficiency of folic acid in the serum is itself the result of impaired absorption of folic acid. Belcher *et al.*, quoted by D. L. Mollin,²⁷⁹ have shown with tritium-labelled folic acid that whereas control subjects absorb an average of 75 per cent of an oral dose of 0.2 mg., patients with idiopathic steatorrhoea absorb only 58 per cent of the same dose.

The biochemical defect which links gluten sensitivity to disturbance of folic acid metabolism has been investigated by Cooke⁸⁰ and by Weijers and van de Kamer.⁴³⁶ The latter authors report that oral loading of gliadin to cases of coeliac disease results in a rise in peptide-bound glutamine in the serum. They postulate that peptides which contain glutamine cause the harmful action of wheat on coeliac disease patients. The presence of these peptides in the blood might be due to genetic incomplete development of the proteolytic enzyme systems in the intestinal cells so that food proteins are not completely broken down to amino-acids but are taken up in the form of peptides.

Cooke⁸⁰ draws attention to the formation of a peptide-pteroyl-glutamate complex which might act as a blocking agent in the folic acid cycle. He concludes with the hypothesis that adult coeliac disease is due to a constitutional enzymatic defect which is closely

allied to folic acid metabolism and which is made evident by administration of gluten. In some patients this defect is so gross that it cannot be corrected even by a diet completely free of gluten.

It may be concluded therefore that there is at present no evidence that dietary deficiency plays any direct part in the ætiology of the steatorrhœas. The genetically-installed enzymic defect does, however, condition secondary malnutrition which is expressed earliest and most markedly through the metabolism of folic acid. The central place of folic acid in the conditioned malnutrition is also strongly suggested by the frequent association of megaloblastic anæmia and by the favourable response of both the anæmia and the malabsorption to therapy with folic acid. The defective absorption of folic acid appears to be very specific. Girdwood,¹⁴⁶ for example, failed to demonstrate any comparable impairment of absorption of riboflavine, aneurine or pyridoxine.

In spite of the conclusion that dietary deficiency plays no direct part in causation, the subject of idiopathic steatorrhœa has been rather thoroughly discussed for several reasons: (1) it illustrates the far-reaching effect of an intestinal lesion in conditioning malnutrition; (2) it suggests that a genetically-installed enzymic defect may make a common constituent of the diet injurious to the intestinal mucosa and so create a vicious circle mechanism; (3) it throws light on one mechanism which may be involved in food allergy (Ch. 14).

The numerous secondary nutrient deficiencies resulting from steatorrhœa and malabsorption syndromes³⁰ are not reviewed here because they are more germane to a textbook of medicine.

CHAPTER 7

DIETARY PROTEINS

THIS chapter is largely concerned with protein deficiency in under-developed regions of the world. The final section (No. 6) attempts to gather together some of the lessons learned from intensive study of this field in the last decade and to apply them to the prevention and correction of temporary states of protein deficiency. The latter often develop under special stresses such as operations and febrile illnesses, even in more privileged groups who ordinarily consume protein foods of satisfactory quantity and quality.

(a) Kwashiorkor

It is less than a decade since the United Nations agencies, WHO and FAO, discovered (a) kwashiorkor as an entity; (b) its origin in protein malnutrition; and (c) its vast world-wide prevalence and importance.^{216, 49}

In human nutrition studies and in international public health, this has been a protein decade.⁴⁴

It started with the recommendation of the Joint FAO/WHO Expert Committee on Nutrition at its First Session in Geneva in October, 1949, that:

“WHO conduct an inquiry into the various features of kwashiorkor including a clinical investigation in the areas where the condition occurs. The object of such an investigation should be to define the clinical features and to study the food habits of the population, with particular reference to diet during pregnancy, lactation, infancy and early childhood. The inquiry should be extended to areas in which the disease does not occur but in which the diet is apparently similar to that of areas in which the disease is found. This may help to establish a correlation between food habits and the occurrence of the disease—its incidence—and define the part played by other factors, such as tropical parasitism, in determining the variations in clinical manifestations.”²¹⁵

As a result of this recommendation a report on "Kwashiorkor in Africa" was presented to the Second Session of the Joint Committee by Brock and Autret.⁴⁹

Other surveys followed and it rapidly became evident that throughout the world there was a vast amount of serious morbidity and preventable mortality in the post-weaning phase of life which arose from the unsupplemented use of starchy foods as post-weaning diets. These diets were deficient either in their total protein content or in their balance of essential amino-acids, but might be calorically adequate. Earlier work in the African continent was reviewed by Trowell *et al.*⁴⁰⁵ and more recently work by Trowell and Jelliffe.⁴⁰⁶

Hansen (Ch. 23) records the contribution of Cicely Williams in Ghana (previously the Gold Coast) in 1933.⁴⁴³

The Third Session of the Joint FAO/WHO Committee was held in Gambia in 1952, and a very thorough consideration of kwashiorkor led to the introduction of the term "protein malnutrition" and its definition (Ch. 7). In the Report²¹⁷ there is an interesting historical appendix giving the names by which the syndrome had been known previously in different parts of the world.

There is an excellent modern review of kwashiorkor with special reference to treatment and prevention in the "1959 World Review of Nutrition and Dietetics."²⁰ The earlier contributions from Central and South America are reviewed in Ch. 21. Work done by our own group in identifying the nature of the deficiency was reviewed in 1959.⁴⁴ The subject has been brought further up to date by Hansen in Ch. 23, which should be consulted for detail and for paediatric reference.

It is agreed that the word "kwashiorkor" means "the deposed child",²⁸¹ since it is a syndrome of post-weaning malnutrition, and that the older interpretation "the red boy" is etymologically incorrect.⁵⁰ The older etymology is also misleading because red hair, although a feature in some pigmented people, is neither invariable nor pathognomonic. The many older names, including malignant malnutrition and infantile pellagra, have been abandoned as misleading. It is historically interesting that on the agenda of the First Joint FAO/WHO Expert Committee on Nutrition there was no reference to protein and the subject was raised indirectly under the heading of pellagra. In Ch. 21 Guzman *et al.* record historically the earlier use in Central America of the term "síndrome pelagroides-beriberico". The term "síndrome pluricarenal infantil" (abbreviated S.P.I.) has been accepted in Central and South America as equivalent to kwashiorkor.¹²³

Kwashiorkor is undoubtedly a disease of multiple ætiology. Over a large part of the rural world, including most of the tropical belt, it is a community problem arising from the following factors:

- (1) predominant cultivation of high carbohydrate staples such as cereals and tubers (especially maize and cassava);
- (2) insufficient production of high-protein foods such as fish, meat, milk and leguminous plants;
- (3) insufficient production of cow's milk for use as a post-weaning food for infants and ignorance of possible alternative post-weaning foods. In many areas cows cannot be kept because of trypanosomiasis;
- (4) ignorance and taboos which result in defective physical and psychological hygiene for the infant.

In urban industrial areas and more developed regions the disease is a social problem resulting from broken and depressed homes.^{139, 283, 295} In all areas it has its roots in poverty and ignorance and should be capable of complete elimination from the world unless population pressure prevents the application of modern knowledge (see Ch. 16). Many factors contribute to its pathogenesis. These include the social influences referred to above. All forms of parasitic, bacterial and virus invasion may contribute and precipitate, especially when they affect the gastro-intestinal tract. The diets on which kwashiorkor develops are deficient in many nutrients, but a group of amino-acids constitute the most-limiting nutrients and cure can be initiated although not consolidated, by solutions containing only amino-acids, glucose and salts (see Ch. 7). Electrolyte depletion and especially potassium depletion are important in precipitating the final breakdown and even death.

(b) Protein Malnutrition

Following the discussion on kwashiorkor two questions can be asked:

- (1) How is man's health adversely affected by wrong quantity or quality of proteins, and how can the wrong trends be recognized and identified?
- (2) What quantity and quality of protein does man require at different ages and under differing environmental circumstances in order to achieve optimum health?

It is unlikely that in the present state of our knowledge we have found the complete answers to either of these two questions, so that any discussion of the practical application of supplementation and enrichment of diets with protein must of necessity be against a background of incomplete knowledge.

It is also necessary to be very careful in our use of terms since, in the field of protein malnutrition, confusion has been created by failure to define terms accurately. In the context of the present discussion we must be particularly careful to distinguish between protein and protein foods (foodstuffs). Protein is a chemical concept denoting a variable combination of amino-acids. There is no one protein. All foods contain proteins in significant quantity with the exception of certain highly artificial foods such as refined sugar and butter. In the past we have been accustomed to talk of "first-class proteins"; it is better now to talk about protein-rich foods (foodstuffs) and the distinction is best expressed quantitatively in terms of grams of protein per 100 calories. In Fig. 2⁴⁹ common foodstuffs are arranged down the right border in descending order of yield of protein per 100 calories. The line of protein requirement per 100 calories is according to the recommendations of the National Research Council of the U.S.A. In practice, if a single food were consumed by an adult for a time sufficient to run down reserves in the body, the cereals would be within the range of real protein requirement expressed in quantity; root products would mostly be quite inadequate; the flesh of fish and mammals would be excessive, while whole cow's milk and leguminous plants would be slightly above requirement. These statements apply, of course, only to quantity. When we add the concept of quality of protein dependent upon amino-acid composition (aminogram) some of the leguminous plants *may* fall down towards the near-adequate or even inadequate range, because of limitations set by the most-limiting amino-acid or amino-acids. The cereals *may* be pulled down by the same limitation to the inadequate range, while the quantitative inadequacy of root products would be magnified. These conclusions depend on the assumption that the line of protein requirement is correctly placed in terms of an ideal or reference protein; hence the word *may*. This is clearly prejudging evidence on which we are unlikely to have final conclusions in the year 1960. It has already been revised downwards in these terms. Fig. 3 represents such a revision in which the protein values have also been given in net figures. The principle is not altered. The validity of the new line of protein requirement is still subject to verdict in the light of further research. The difficulties

of the FAO Committee¹²⁶ on a reference protein are more than apparent. Comparison of the FAO reference pattern and whole egg in man by nitrogen balance was adverse to the FAO pattern.⁴³⁵

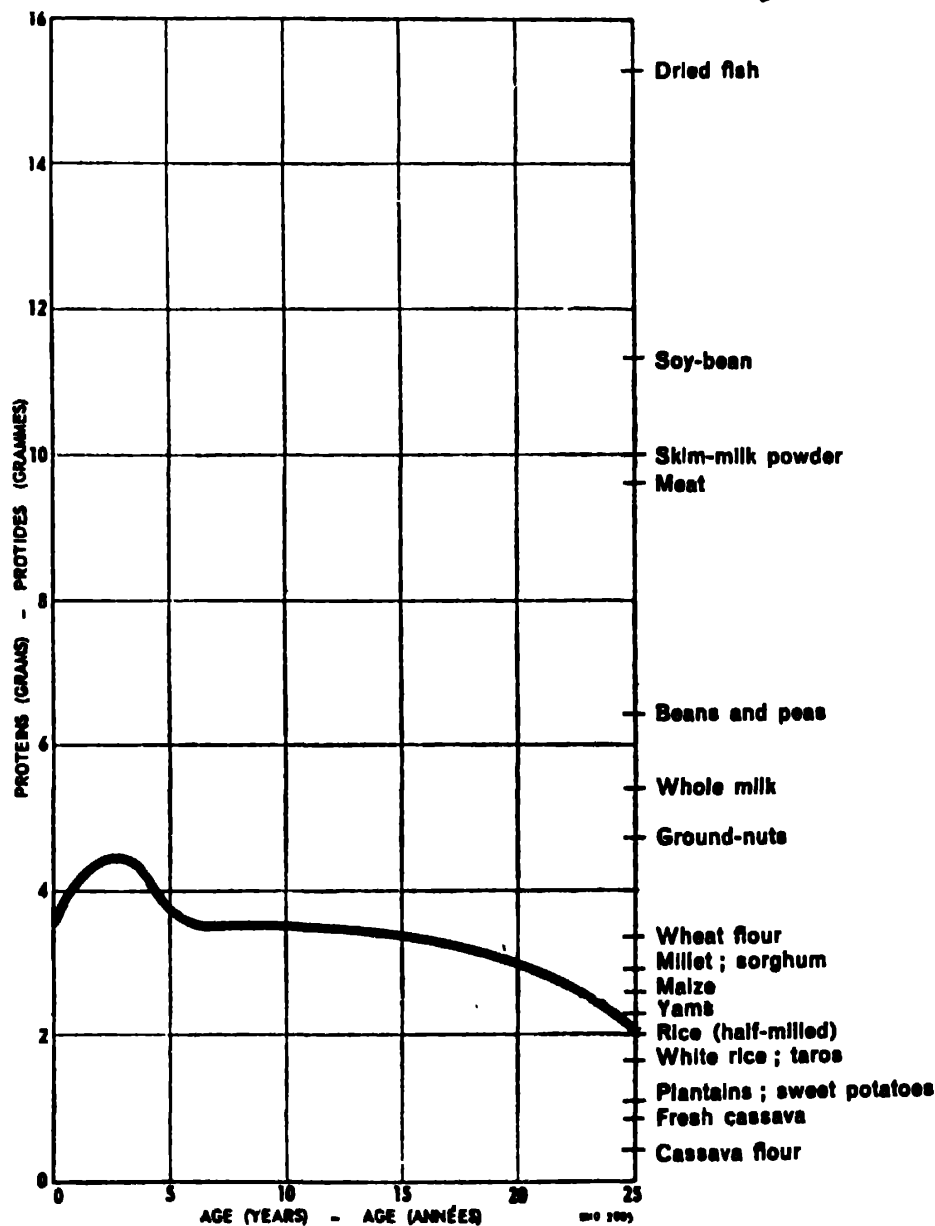


FIG. 2. Curve of requirement of protein per 100 calories according to age; yield of protein per gram of common foods (right-hand margin). Reprinted from "Kwashiorkor in Africa." ⁴⁹

Another term which has been repeatedly misunderstood and which has therefore led to psychological resistance is "protein malnutrition". Many of the people who show this resistance appear never to have read the definition of protein malnutrition given by

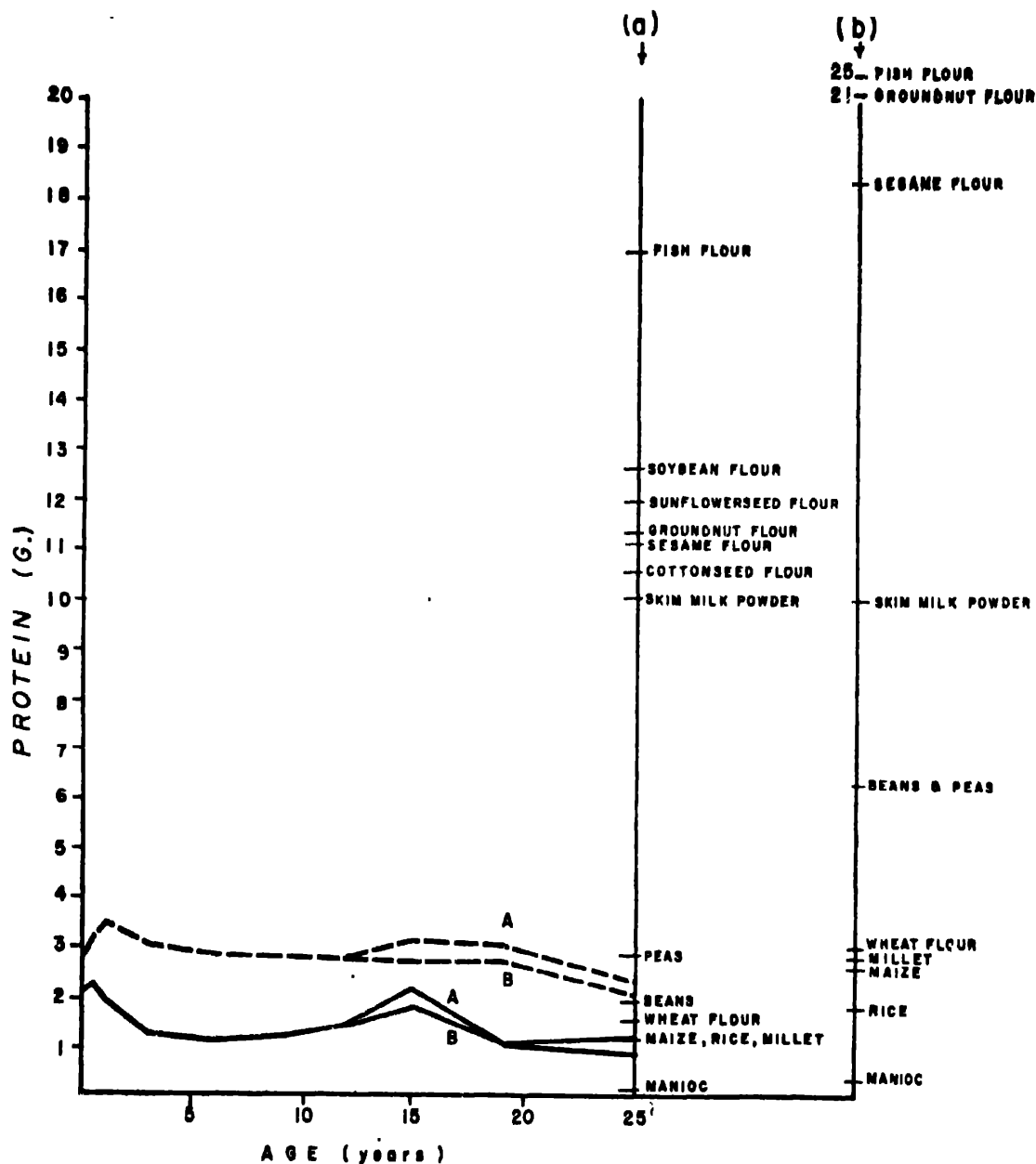


FIG. 3.

— Requirements in terms of FAO reference protein (including allowance for individual variations).
 - - - NRC allowances.
 A Females.
 B Males.

On the right hand side of the figure is indicated the yield of protein per 100 calories of some foodstuffs in terms of (a) net protein value, (b) crude protein.

Protein requirements per 100 calories according to age; recalculation by Autret¹¹ of Fig. 2. Comparison of the solid line in this figure with that in Fig. 2 shows the extent to which estimated protein requirement has been reduced in 10 years through advancing knowledge of the effect of protein quality on protein requirement. The reduction and requirement has, however, been offset by recalculating crude protein in terms of net protein value. The net result is that the cereals remain marginally adequate for the adult and remain inadequate for the infant and young child.

the Joint FAO/WHO Expert Committee on Nutrition in 1953. In 1959⁴⁶ I repeated the definition and drew attention to the fact that after careful reading it remains ambiguous only in one small respect, namely in the use at one point of the term "protein" when the term "protein food (foodstuff)" should have been used. It is clear from the context that the definition was intended to convey a public health rather than a scientific concept, and was intended to denote a state of malnutrition resulting from deficiency of protein-rich foods while calories are provided in relative excess, or even to optimum level, through starchy foods. The resultant malnutrition will express itself through deficiency of many nutrients including many, if not all the essential amino-acids, many vitamins and perhaps trace mineral elements ordinarily supplied in the human diet by protein-rich foods (including perhaps especially vitamin B₁₂ and folic acid). The Central and South American term S.P.I. (síndrome pluricarenal infantil) has value in indicating that kwashiorkor is a multi-nutrient deficiency. On the other hand, the same multiplicity concept was inherent in the original definition of "protein malnutrition" which developed out of the consideration of kwashiorkor. A critical study on initiation of cure in kwashiorkor⁵⁴ including a later report on the reversal of the pellagroid dermatosis¹⁶⁹ on a synthetic formula containing amino-acids, glucose, electrolytes and water without any vitamins, has been widely accepted as demonstrating that the most-limiting nutrients are a group of amino-acids.²⁰ This seems to imply that the basic cause of kwashiorkor is deficiency of a group of amino-acids ordinarily supplied in the diet of developed or privileged communities through protein-rich foods, even though at the same time there is inevitably a deficiency of other nutrients, including vitamins. In other words, we can now add to the public health concept that kwashiorkor is a result of protein malnutrition, the scientific concept that it is due primarily to relative deficiency of proteins.

Nevertheless, the term *protein malnutrition* has not given general satisfaction. In Ch. 21 Guzman *et al.*, discussing the S.P.I. syndrome (síndrome pluricarenal infantil), refer to Gomez' classification into first, second and third degree malnutrition. This classification was intended to denote a wide approach to a spectrum of states of malnutrition in young children emphasizing deficiency of other nutrients (which nevertheless are included in the term "protein malnutrition" as defined) and even non-dietary ætiological factors which are accepted by all workers in this field. This classification has not won general acceptance, but has a certain value.

More recently Jelliffe²¹³ introduced the term *protein-calorie malnutrition*. This term has the merit of emphasizing the close connection which exists between calorie and protein requirements. It has the additional merit of being wide enough to cover not only kwashiorkor but marasmus and the spectrum of malnutrition in young children which lies between these two clinical entities and which has been loosely termed *marasmic kwashiorkor*. The subject has been further developed by Bengoa *et al.*²² under the title: *Some indicators for a broad assessment of the magnitude of protein-calorie malnutrition in young children in population groups*.

Protein malnutrition was the subject of a conference in Jamaica in 1953⁴³¹ In 1955 a similar conference was held at Princeton, N.J., U.S.A., under the title: *Human protein requirements and their fulfilment in practice*.⁴³⁴

The Joint FAO/WHO Expert Committee on Nutrition at its Fifth Session in October, 1957, devoted considerable time to reviewing progress in protein malnutrition and preventive measures.²¹⁸ The Committee was concerned particularly with "studies necessary to evaluate the safety and effectiveness of high-protein foods, and to test the practical usefulness of such foods, or mixtures of them, in the prevention and treatment of protein malnutrition in various regions". It laid down the following criteria "for the selection of protein-rich foods other than milk which are worthy of inclusion in this programme of study: (a) they must be available or capable of being produced locally; (b) their production and purchase by all sections of the population must be feasible from the agronomic and economic standpoints; (c) they must be easily transportable and have a long storage life without refrigeration under prevailing conditions of heat and humidity; (d) they must be free of any toxic or other deleterious factors; (e) they must be acceptable as regards taste, odour, and physical properties, and easily included in ordinary diets; (f) their nutritive value with respect to protein must be such that they effectively supplement existing diets".

An important reference is the Report of the Committee on Amino-Acids of the U.S.A. National Research Council (1959).⁷⁹ At the time of completion of the manuscript of this book, the most recent comprehensive review is that of a symposium on: *Protein requirement and its assessment in man*.³⁹⁵ The communications covering pp. 1125-1211 are very comprehensive and contain an up-to-date bibliography. More important, however, is the discussion occupying pp. 1212-1231. The Chairman remarked that the unusual technique used in that symposium should be considered as a trial and rehearsal

for a symposium planned as the backbone of the programme for the Fifth International Congress on Nutrition to be held in Washington, D.C., September, 1960.*

(c) Protein Requirements

The general problems of fixing recommended allowances in relation to minimum and optimum requirements (Ch. 11) is well exemplified in the problem of protein requirements. In the 19th century Voit fell into the error⁴² of concluding that because the average German worker consumed 120 g. of protein per day, this was likely to represent his optimum requirement. In the first half of the 20th century, it was recognized that requirement for protein depended very much upon quality of protein, and protein foods were divided into those of animal and vegetable origin or alternatively into first and second-class proteins. With this new outlook it became customary to recommend 1 g. of protein per kg. of body weight provided at least one-third of the protein was of animal origin. Thus the Health Committee of the League of Nations³⁹⁸ recommended as follows: "In practice, the protein intake for all adults should not fall below 1 gramme of protein per kilogramme of body weight. The protein should be derived from a variety of sources and it is desirable that a part of the protein should be of animal origin. During growth, pregnancy and lactation, some animal protein is essential, and in the growing period it should form a large proportion of the total protein."

With the advent of the United Nations Agencies in the 1940s it became increasingly apparent that conventional recommended allowances of protein were not being achieved by a large part of the underprivileged world and that there was very little likelihood of their being so achieved. In re-examining the recommended allowances for protein of the U.S. National Research Council in 1946, Hegsted *et al.*¹⁸² carried out nitrogen balance studies on 20 adults in apparent good health. Two diets were used. The first was devoid of animal protein, the protein being supplied to the extent of 50 per cent by white bread with the balance divided between other cereals, vegetables and fruit. In the second diet one-third of the

*At the time of this writing the communications of the invited speakers to this International Congress are already in the hands of the author of this monograph in his capacity as prospective moderator of the discussion. They are referred to in this chapter. The more important discussion will be summarized, together with other highlights of the International Nutrition Congress, in an appendix chapter.

protein was replaced by meat. Both diets were believed to be adequate in respect of calories and other protective nutrients. From these studies they concluded that nitrogen requirement is more closely related to surface area (basal caloric expenditure) than to body weight. They estimated the requirement for maintaining nitrogen balance on the two diets to be respectively 2.9 g. (18 g. conventional protein) and 2.4 g. (15 g. conventional protein) per square metre of body surface. They calculated that a man weighing 70 kg. would require between 30 and 40 g. of protein of purely vegetable origin and that when meat was added the protein requirement would be reduced by approximately 17 per cent. They concluded also that the biological value of the all-vegetable diet was increased from 72.5 to 80.4 by replacing one-third of the protein with meat. They found the digestibility of the two diets to be essentially similar. Apart from nitrogen balance they concluded that there was no deterioration in the physical condition of the subjects during the studies, although some of those on the vegetable diet complained of post-prandial hunger and fatigue while those on the meat-containing diet had no such complaint. They found no significant changes in hæmoglobin, hæmatocrit or plasma volume, but total protein, plasma albumin and plasma globulin tended to decrease on the low-protein all-vegetable diet. When this diet was fed at a level low enough to produce negative nitrogen balance, the replacement of one-third of the protein in the all-vegetable diet by meat resulted in a prompt increase in the globulin fraction. They emphasized that their conclusions applied only to adults in apparent good health and did not apply to the protein requirements of growth, pregnancy, lactation or disease. They concluded that "the National Research Council's daily recommended allowance of 70 g. of protein for an adult weighing 70 kilograms is most generous and could, if necessary, be reduced to 50 g. and still provide approximately 30 per cent margin above requirement".

Hegsted¹⁸¹ has brought his views on minimal needs of protein up to date. His Table 2 sets out accepted figures for various ages and an appropriate adjustment for proteins of lower biological value (represented by B.V.70). The older approach reviewed in this chapter is still useful for understanding the subject.

With increasing understanding of the variability of the amino-acid pattern (aminogram) of different protein foodstuffs and of infant and adult requirements of individual amino-acids^{196, 338, 373, 374} it becomes necessary to consider, at least for underprivileged populations, a minimum requirement for each individual amino-acid.

This newest approach resulted in the 1957 Report of the FAO Committee on Protein Requirement.¹²⁶

This report covers some fundamental principles such as the term *nutritive value of a dietary protein* and the relationship of the latter to *biological value*, *replacement value*, *nitrogen balance*, and *nitrogen balance index*. The Committee emphasizes that wherever consideration is being given to the nutritive value of protein or of combinations of amino-acids it must be recognized that "the utilization of amino-acids by the body is affected also by calorie intake, by the relative quantities of carbohydrates and lipids, by the nature and quantitative distribution of minerals, and by the absence or abundance of various vitamins. Furthermore, the value of a given quantity of protein varies considerably according to whether the whole is ingested during a single meal, or whether its ingestion is distributed over several meals. The utilization of amino-acid thus depends on the nature of the diet as a whole, the timing of meals, and the efficiency of digestion and absorption from the gastrointestinal tract."

The Committee decided to express requirements in terms of a protein of high nutritive value defined by putting forward examples of proteins which fall into this category. The examples taken are "the proteins contained in milk, eggs and meat, which have long been regarded on the basis of observation reinforced by research on infants and adults, as being of excellent value for human beings". It has also put forward a *provisional amino-acid pattern* which does not correspond precisely to that found in milk and egg protein. It is "assumed that a hypothetical protein containing amino-acids according to the pattern will be a protein of high biological value falling into the reference category". This definition is, of course, based on some unproven although reasonable assumptions. The Committee then put forward (Fig. 4) a "curve showing average minimum requirements for the reference protein, per kilogram of body weight, by age".

A footnote indicates that the curve is applicable only "under the following conditions:

- (1) That all protein is supplied as protein of high nutritive value.
- (2) That no significant losses of protein occur through incomplete digestion.
- (3) That the diet does not vary greatly from meal to meal and meals are evenly spaced.
- (4) That disease and parasitic infection are absent".

It further emphasizes "the tentative nature of the curves in the figure".

An adult requirement of 0.35 g./kg. was suggested for this reference protein. Factors were suggested, based on the biological value of different proteins, which could be used to give the equivalent

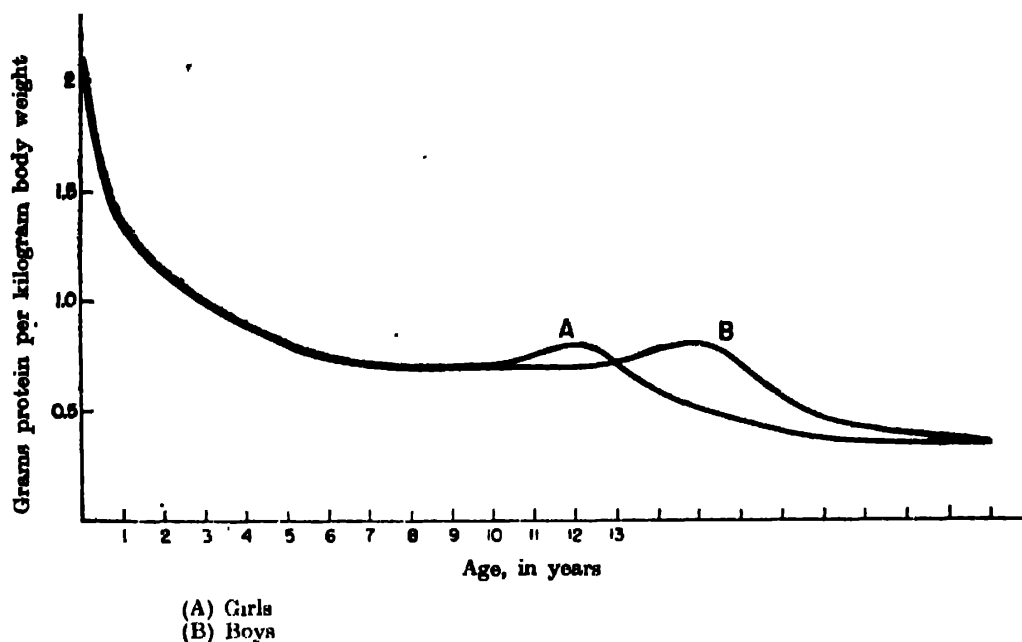


Fig. 4. Protein requirements as g./kg. Reprinted from FAO Nutritional Studies No. 16, 1957. "Protein Requirements," FAO, Rome.¹²⁶

requirement of other proteins in relation to the minimum requirement of the reference protein. Thus for a protein food with a protein score of 70 the minimum requirement would be 0.35 divided by 0.70 equals 0.5 g./kg./day. For this approach, the method of determining the protein score of any protein becomes important. This matter is discussed in Ch. 28.

This report has been freely quoted because it deals with a fundamentally new approach to protein requirement based on modern knowledge of amino-acid requirements.

In 1955 Rose and his colleagues³³⁸ published article No. 15 in a long series of studies on the requirement by man of individual essential amino-acids. In a succeeding paper Rose and Wixom³³⁷ take up the problem of the requirement of non-essential amino-acids needed to supplement and economize the eight essential amino-acids against the background of an otherwise adequate intake of calories and other known nutrients. They proceeded by adding to the diet both urea and glycine to provide initially a total daily intake of

exactly 10.00 g. After allowing time for a preliminary adjustment to the diet, the state of the nitrogen balance was determined for a period of six days. The nitrogen consumption was then progressively decreased, first by removing the urea from the ration, and then by excluding part of the glycine. This process was repeated until the minimal amount of nitrogen compatible with a distinctly positive balance was established. On the basis of these studies, Rose and Wixom came to the conclusion that in a well-balanced mixture of essential amino-acids with glycine as a source of non-essential nitrogen there was a remarkable economy in the utilization of nitrogen to the extent that a total daily intake of 3.50 g. N ($6.25 \times 3.50 = \pm 22$ g. protein) is sufficient to maintain nitrogen equilibrium and that the figure might possibly be as low as 2.55 g. daily (± 16 g. protein).

Holt and Snyderman have made an equivalent study of the minimum quantity of milk required by infants. They expressed it in terms of percentage of calories from protein. The critical lower level in two infants was 6 per cent of calories as protein.³⁷⁴

Reference has been made in Chs. 7 and 23 to the ease with which kwashiorkor can be cured by synthetic mixtures of amino-acids with glucose as a source of calories and with added vitamins. In fact cure can be initiated in kwashiorkor even if the vitamins are omitted. It seems therefore that we may be within sight of a situation in which reasonable nutrition, if not perfect health, can be achieved with synthetic amino-acids as a sole source of nitrogen. The work of Rose and his group on young healthy adult males and of Holt and his group³⁷⁴ on infants suggests this possibility. It must be emphasized, however, that knowledge on amino-acid requirements is by no means final. It has been known since the investigations of Rose that caloric needs are higher for isonitrogenous diets of synthetic amino-acids. Some comparative figures have recently been given.⁸¹ It is dependent, at least as it applies to man, too much on nitrogen balance data. Some other problems were discussed in a symposium at the University of Rutgers in 1957.⁷⁷

It may well be true that an adult human can maintain nitrogen balance on 0.35 g./kg./day, but the limitations of nitrogen balance in relation to the uncalculable factor of loss of nitrogen from skin must be remembered.^{166, 409, 410} Even if true nitrogen balance is maintained on this allowance, there is the possibility that the body may have adapted itself to a suboptimal nitrogen intake which is not consistent with optimum health and resistance to disease. Yoshimura⁴⁵⁹ suggests that this may be achieved by the double

mechanism of reducing the reserve protein in the body and decreasing the rate of protein catabolism.

It is worthwhile for students of this subject to go back to the pioneer paper of Folin¹³⁰ on a *Theory of Protein Metabolism*. Later developments are reviewed by Patwardhan.³¹³

Relationship of Protein Requirement to Intake of Calories and other Nutrients. The discussion on human protein requirements up to this point has been based on the assumption that calories and all other required nutrients were provided by the total mixed diet consumed. Attention should be drawn at this point to Ch. 28 in which Platt, Miller and Payne stress the fallacy of the assumption that "the biological value of a protein is something static". It can, of course, only be considered in relation to a defined total intake of calories and other nutrients. Where calories from carbohydrates and fat are deficient, protein is deaminized and used as a source of calories—a most wasteful procedure. The appropriate sections in Platt's Ch. 28 should be consulted as well as the author's section on *Supplementation and Enrichment with Protein* (Ch. 7).

The Effects of Marginal or Low-protein Intakes. There is growing evidence that the economy procedures suggested by Folin do in fact operate and that healthy reserves and resistance may thereby be impaired.^{243, 244, 412} It is by no means proven that the minimum requirement for the maintenance of nitrogen balance is the same as the optimum requirement for the maintenance of health even without conditions of stress. Many questioning voices have been raised about the implications of intakes as low as 0.35 g./kg./day. Our own observations in this field suggest that the serum albumin is sensitive to declining reserves and that there is a level which we have called "marginal hypoalbuminæmia" which indicates declining protein reserves without other manifest evidence of protein deficiency (Ch. 7).

Yoshimura⁴⁵⁹ has recently carefully analysed the effects on Japanese subjects of what he regards as marginal intakes of protein in the diet. He has shown the effect of such diets on the level of serum albumin and hæmoglobin, the latter through some degenerative process in the erythrocyte membrane and expressed through decreased osmotic resistance to saline. Among other evidences cited by him as representative of marginal levels of dietary protein intake are the appearance of urobilinogen in the urine and reduction in the activity of various enzymes in the liver. He believes that hormonal activities are also depressed. The diets used contained 0.57 g./kg./day of protein. In one diet the protein was mainly of animal origin (protein

score 96) while in the other it was mainly cereal protein. In this latter diet the protein score was 63 and the limiting amino-acids were tryptophane and methionine. Evidence of impaired reserves and impaired vitality developed on both diets but more quickly on the latter than on the former. He examined also the effects of hard physical labour. Taking all factors into account, he believes that for the Japanese diet an intake of 1.25 g./kg./day of protein is a practical allowance for adults. Yoshimura's evidence is carefully collated and, coming from a nation such as Japan which is notorious for its economy in food utilization, it must be taken seriously. Nevertheless, one must be forgiven a residuum of scepticism over this immoderate swing of the pendulum from 0.35 to 1.25 g./kg./day. Some of the changes described by Yoshimura in serum albumin, hæmoglobin and erythrocytes might have been due to shifts in plasma volume and the possibility of marginal deficiency of hæmatinic nutrients such as iron and folic acid have not been excluded.

Decision must be left until we have more reliable methods than are at present available for the recognition of human protein deficiency. In any case the quantitative requirement is dependant on the quality of the protein and the rest of the dietary and other environmental context (Ch. 7). The same considerations are emphasized in the final paragraph of Platt's chapter (Ch. 28).

(d) Recognition of Protein Deficiency

At a meeting of WHO Nutrition Consultants research problems in this field were reviewed. One of the items listed was "methods for the measurement of the degree of protein depletion and a study of the significance of protein stores". This problem is fundamental and answers must be obtained before real progress is made in any other field. It is clear that there is no clinical method of recognizing human protein malnutrition or protein undernutrition except when it is well advanced. In post-weaning infants, for example, the clinical picture and laboratory criteria of kwashiorkor are well defined, but those of "prekwashiorkor" are very uncertain. Prekwashiorkor, even if recognizable, is, nevertheless, probably already a well-advanced stage of protein malnutrition and it is the earlier and milder subclinical stages which we want to recognize by laboratory tests. The problem is even more difficult at other ages, since protein requirements are highest in the first five years of life.

It is clear that we still sadly lack objective clinical and biochemical tests for the demonstration of states of protein deficiency in

the human being, at least when the deficiency is mild. My own group has been active in this search for several years, with only partial success. We feel, nevertheless, that progress has been made, and that we are within sight of means for recognizing these milder protein deficiency states.

Biochemical Recognition of Protein Deficiency. In a series of papers published or in press, we have reported the work of several years, which will be summarized here.^{166, 168, 170, 343-46.}

In comparing formulæ for their efficacy in "initiation of cure in kwashiorkor" we have used regeneration of serum albumin as our most sensitive biochemical index. It is not as sensitive an index as the reticulocyte count in assessing the efficacy of different batches of liver extract in the treatment of pernicious anæmia, but it is probably as sensitive as the hæmoglobin which was put forward as a mathematical index.²⁷⁸ Regression lines for regeneration of serum albumin constitute a very effective mathematical expression of the comparative efficacy of formulæ when used on sufficiently large groups of cases of kwashiorkor.⁵⁴

It appears to me to follow from this that there must be a marginal range of hypoalbuminæmia which can be used as evidence of impending or early protein deficiency. One can say by analogy that it is now generally accepted that levels of blood hæmoglobin between say 12 and 10 g. per cent associated with a low M.C.H. constitute presumptive evidence of iron deficiency. If a group of subjects with hæmoglobin within that range is treated therapeutically with iron, and if their mean hæmoglobin level rises from the range indicated to a range, say, between 12 and 14 g. per cent, most people will accept this as evidence that the majority of that group of individuals, and certainly those whose hæmoglobin level rose appreciably, were suffering from a state of iron deficiency which has now been corrected. Applying this analogy to hypoalbuminæmia and protein feeding, we believe that our results in initiation of cure of kwashiorkor establish a range of hypoalbuminæmia which is certain, in the absence of serious complications, to be improved by feeding with a good protein-containing formula. We have examined our records over several years, and can define (Fig. 5) for our own laboratory and environment, and for children between the ages of 2 and 10 years, figures for that range of 2.75 to 3.50 g.³⁴⁶ The figures, of course, apply only to the age and environment indicated and to our own laboratory method (27 per cent sodium sulphate precipitation and Biuret determination). Comparable figures could be established for any other method and any other environment.

Compared with serum albumin, other biochemical indices have been found either inferior or less easily applicable. This conclusion applies to serum total cholesterol,³⁴³ serum amylase³⁵⁵ and serum globulin. Although erythrocyte counts and hæmoglobin determinations are almost invariably low in kwashiorkor, we have not found them to constitute sensitive evidence of protein deficiency, probably

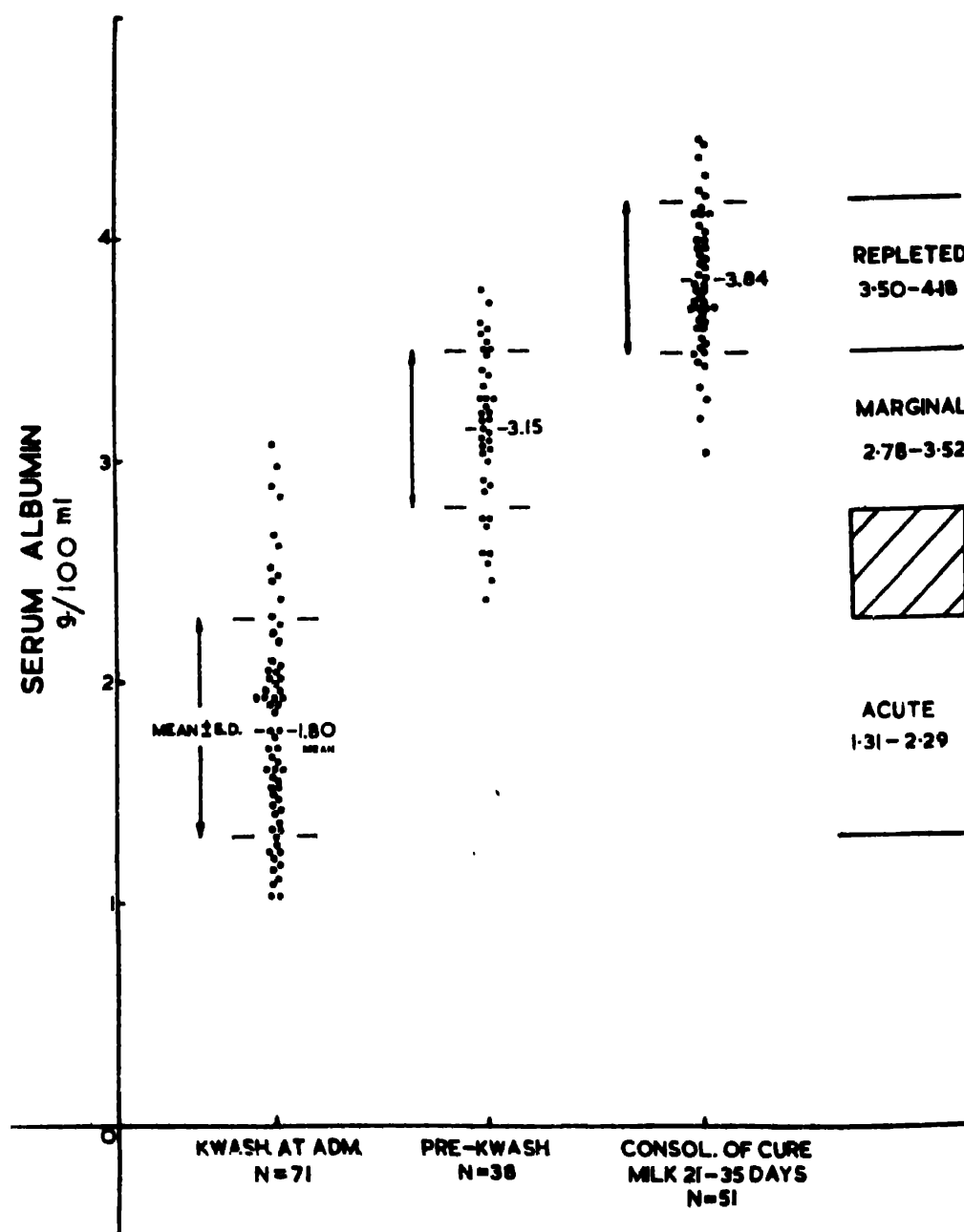


FIG. 5. Three stages of protein nutrition in infants and young children with their related serum albumin concentration (mean \pm S.D.). The children used to define the marginal range were subjects who had received a low protein diet and who were beginning to demonstrate incipient symptoms of kwashiorkor.³⁴⁶

because of the frequency of associated deficiency of iron, folic acid or even vitamin B₁₂. Yoshimura's contrary view is discussed above.

We have devoted several years' work to the examination of nitrogen balance as a method of detecting protein deficiency in both infants and children.^{166 170, 409, 411, 412} Our reluctant conclusion from this very arduous work is that although the study of nitrogen balance is very informative in the understanding of protein metabolism it is not by itself a sensitive indicator of protein deficiency because it is influenced by too many uncontrollable variables and because the loss of nitrogen through sweat and desquamated epithelium cannot be quantitatively measured. It can be roughly estimated, nevertheless, under standard conditions of temperature and humidity. Nitrogen balance, nevertheless is a valuable method for comparing the nutritive value of iso-nitrogenous quantities of different formulae.

Our findings and conclusions on urinary nitrogen partition and body composition are discussed in a communication to the Fifth International Congress on Nutrition, 1960, and can be summarized here by saying that in the existing state of our knowledge and understanding these are not likely to give us the routine information we want. Low figures for 24-hour urea excretion do, of course, indicate a low intake of protein in the diet, but this information applies at the most to the diet of the last two days, and does not indicate anything about the state of protein reserves or protein nutrition.

In summary, therefore, we must conclude that in the present state of our knowledge, the earliest and most sensitive biochemical index of mild or impending protein deficiency is a drop in serum albumin into the marginal range. Causes of abnormal protein loss such as proteinuria, hæmorrhage, burns, or of failure of protein synthesis (liver failure), must, of course, be eliminated. The significance of the hypoalbuminæmia must be clinched by demonstrating the return of the serum albumin to the normal range under the influence of good protein feeding.

The Clinical Recognition of Protein Deficiency. It is doubtful whether it is possible in the present state of our knowledge to identify early protein deficiency by any sort of clinical observation or examination. The approach to this problem must be against the context of the clinical results of malnutrition of any type. The subject has been discussed in general in Ch. 5.

The most obvious evidence of reversible clinical disturbance from protein deficiency is in community statistics for growth in weight

and height after weaning. In regions where protein malnutrition is endemic, infant growth is normal or near normal up to the time of weaning. It then falls steadily behind comparable curves for children in developed nations and well-nourished communities for a

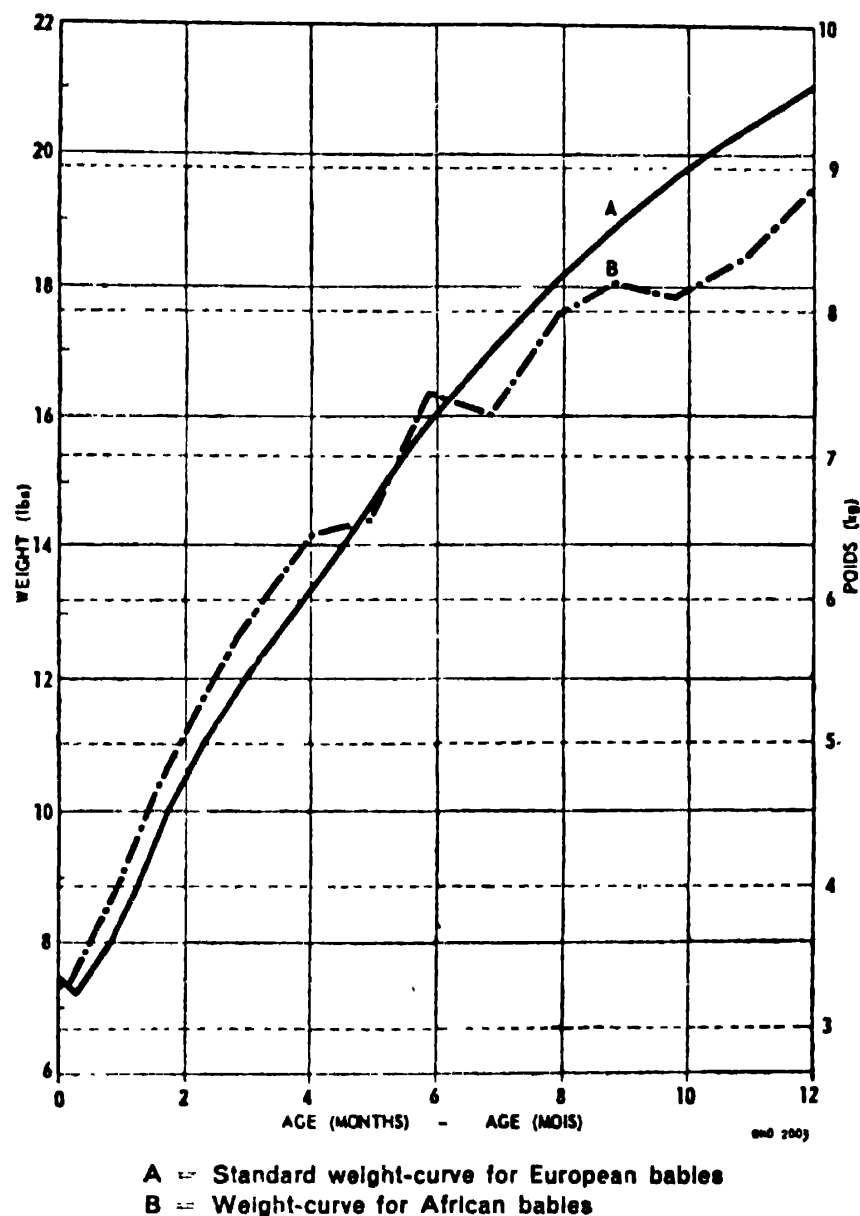


FIG. 6

FIGS. 6 and 7. Effects of protein malnutrition on growth in weight during infancy and early childhood. Reprinted from "Kwashiorkor in Africa."⁴⁹ Note deviation of curves after age 6 months.

few years, after which it slowly accelerates towards the normal curve, but never completely catches up (see Figs. 6 and 7). The maximum deviation from normal in these curves covers the period of maximum incidence of kwashiorkor and is undoubtedly due in

part to protein malnutrition which tends to be corrected after the age of 5, as the child becomes more mobile, develops teeth, and can compete with the rest of the family for a share in the family protein supplies. Unfortunately, there are so many other causes of

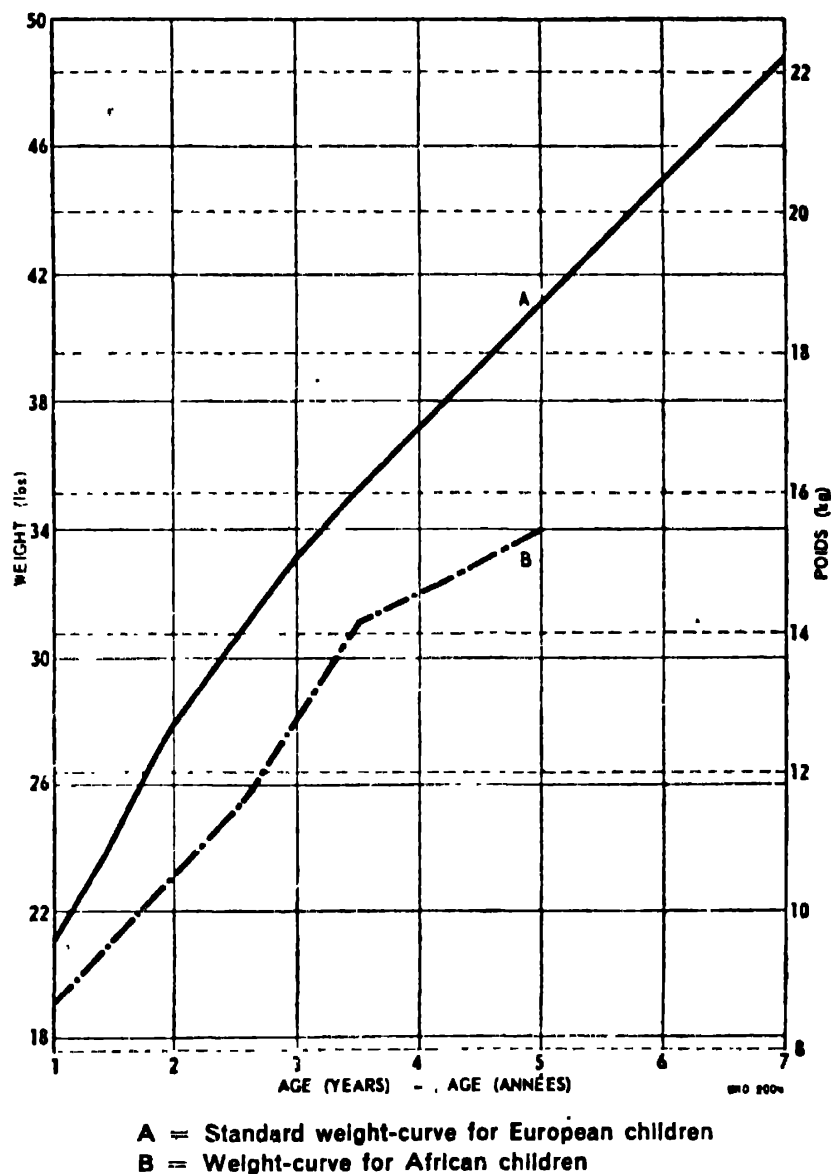


FIG. 7

failure in growth, including calorie deficiency, other forms of malnutrition, and parasitic and infective diseases, that these curves cannot be used as measures of protein deficiency even in group statistics, much less in the individual.

There are no specific effects of protein deficiency on mucous membranes or skin and its appendages comparable with those which are described for vitamin deficiency; or rather they cannot be

distinguished. The same difficulties as are described in regard to the recognition of reversible clinical syndromes of protein deficiency apply also to irreversible structural damage. The part played by protein deficiency cannot be distinguished from the effects of other deficiencies and of diseases due to parasitic and infective invasions.

What might be called protein subnutrition is not recognizable in the absence of biochemical abnormality. We are therefore confined to the appearance of biochemical abnormality for the recognition of protein subnutrition. Reasons have been given above for regarding hypoalbuminaemia as probably the most sensitive of these biochemical abnormalities. Constitutional susceptibility from chronic protein malnutrition was reviewed in 1955 and 1959^{40, 46} (Chs. 4 and 14). In summary, many diseases are encountered in tropical under-privileged communities, which are not encountered or only rarely encountered among privileged communities in temperate climates. Most of these appear in adult or middle age and are obviously multiple in aetiology. Their occurrence within tropical regions suggests that tropical parasites and infections may represent an important contributory cause. However, quite often the same diseases are seen in underprivileged communities living right outside the tropical belt and free from the strictly tropical parasites. This suggests that some non-tropical factor must play a very important part. Malnutrition and especially protein malnutrition has a lot to commend itself as one of the important factors since the world distribution of many of these diseases is very similar to the world distribution of kwashiorkor.

The problem is best exemplified in the case of endemic primary carcinoma of the liver, arising in an insidious, symptomless cirrhosis of the liver with maximum onset between the ages of 20 and 40 years.^{24, 39} The nature of the cirrhosis is discussed in Ch. 13.

(e) **Supplementation and Enrichment with Protein**

The prevention or correction of protein malnutrition takes us to the heart of the problem involved in the use of the terms *enrichment*, *fortification* and *supplementation* as applied to foodstuffs and diets. There has been, and still is, ambiguity about the use of these terms.

It is suggested that the term supplementation be used solely in relation to a meal or a diet, whereas the terms fortification and enrichment be used solely in relation to a food (foodstuff) whether in a natural, prepared or processed form. Thus when fish-paste or peanut butter are spread on a slice of bread, the nutritive value of the bread is being supplemented. If, on the other hand, fish flour or

peanut flour are incorporated in the bread before it is cooked, the bread is being enriched or fortified. Of the two terms *enrichment* and *fortification* the former seems the more suitable in common English usage, while prevailing nutrition usage appears to have made no valid distinction between them. The term fortification is therefore dropped from the present discussion, although it has been used by Flodin in relation to the addition of synthetic amino-acids to foods.¹²⁹

Western mixed diets are based on the principle of enrichment of staple foodstuffs, although this has been worked out over centuries in relation to palatability and only in the modern era has come to have nutritional significance. Originally people spread butter on bread because it was more palatable. Now it is recognized that the butter contains important fat-soluble vitamins and that because of the high calorie yield per g. of fat it reduces the bulk of the bread which would have had to be consumed to achieve the same calorie intake had butter not been spread on it. In the modern era of urban residence, sandwiches have become an important part of the diet of those who are not able to come home for a mid-day meal. For such people supplementation of bread with butter gives not only greater palatability but greater nutritive value. This modern use of sandwiches in urban communities also accounts for the drift towards wheat as a staple among those who, in their rural life, used other staples such as maize. This is noticeably true of the Bantu in South Africa.

Another method of supplementation has been applied by the gold-mining industry of Johannesburg in the Union of South Africa. Owing to Bantu traditional dependence upon maize as the main source of nutrients, "protective" foods have been incorporated in a meat stew and served with maize porridge.^{74, 350} This is clearly supplementation of a meal or diet. On the other hand, soya bean and other sources of protein have been incorporated in *mahewu*, a non-alcoholic fermented millet gruel to which the Bantu are very partial. These supplements or enrichers have even been incorporated in a commercial dehydrated mahewu powder.^{318, 356} This brings supplementation very close to enrichment.

For several decades, Western countries have recognized the possible adverse effect of the milling of cereals, e.g. white flour, white rice and white maize. Nutritionists and dietitians have failed to persuade populations to go back to the obviously more nutritious whole grain for reasons which involve considerations of palatability, appearance, social status, storage, etc. It became customary there-

fore to enrich the white flour, etc., with those nutrients which had been removed in the process of milling, e.g. thiamine, niacin and iron. This seems to be an acceptable procedure although there are still many who complain either that not all of the substances removed have been replaced, e.g. cellulose, or that some unknown factor has been removed from the original grain. This latter belief seems to underlie the "back to nature" forms of dietary faddism.

A more recent development has been the addition to staple foodstuffs, before processing, of foods or nutrients which are judged by health authorities to be relatively deficient in the diet of a population because of too great dependence on the staple foodstuff. This idea underlay the incorporation of protein-rich foods in cereal products such as bread.²⁹⁴

On the general subject of food enrichment the report referred to makes some useful conclusions and recommendations after a study of policies adopted in the United Kingdom, the United States of America, and recommendations by FAO and WHO. Because of their general value and relevance to this discussion, they are reproduced in full. It is suggested that evidence of the following kinds should be available before programmes are embarked on :

- (1) Evidence that there is a need for the nutrients to be added by enrichment.
- (2) Evidence that the enrichment of a staple food has advantages over the use of natural foods as a means of improving the diet.
- (3) Evidence that the amounts of enriching substances provided are sufficient to satisfy the proven need.
- (4) Proof that the enrichment medium is regularly consumed in important quantities by those in need of enrichment.
- (5) Evidence that enrichment can be easily carried out in practice.
- (6) Evidence that the enriching substances or preparations do not appreciably alter the appearance, taste or physical characteristics of the medium.
- (7) Evidence that the enriching substances or preparations are free from bacterial contamination and toxicity.
- (8) Evidence that the cost of the enriching materials is low in relation to their nutritive value.
- (9) In cases where all the nutritional deficiencies present are not satisfied simultaneously, evidence that the particular enriching nutrients used will not fail to exert their beneficial effects.

A thoughtful study has been published by Gilbert and Gillman of methodological problems and interpretations affecting supplementation as applied to maize.¹⁴² Their study has been made on male and female rats, but many of the interpretations may be valid for man. They found that sexual maturity and longevity could be attained by rats fed diets promoting at least three different patterns of growth, namely (1) slow growth with a low maximum weight; (2) rapid growth, similar to the controls; and (3) growth in excess of the controls. They emphasize the importance of not drawing deductions simply from growth rates (Ch. 14), but also from length of survival and freedom from gross organ pathology. On the basis of a long series of experiments they draw attention to the need to consider the whole spectrum of nutrients before interpretations are made on the value of the addition of protein-rich foods to staple carbohydrates such as maize. They found, for instance, that soya bean could only be used to advantage by the growing rat provided that a salt mixture, vitamin B complex and vitamins A, E and D were also added. Even then, supplementation with soya bean, unlike skimmed milk powder, tended to promote a high frequency of kidney lesions and particularly nephrocalcinosis. In other words, "skimmed milk powder complemented in every way the various ingredients of maize in contrast to soya bean which, though providing a useful source of protein, aggravated the mineral imbalance and emphasized the vitamin A requirements."

This paper does not give the necessary data on controls and statistical analysis necessary for critical evaluation of results. In particular, data are not given on food consumption in experimental and control groups adequate for conclusions on palatability of diets, nor are quantitative figures given on reproductive ability. The conclusion, "skim milk is the only natural food which alone can significantly improve the nutritive efficacy of an exclusively maize diet" although correct for the field of the authors' experiments is a misleading generalization since they did not test, for example, meat or fish.^{21, 127} They came to the final important conclusion "that while a knowledge of the chemical composition of a food afforded useful clues as to its possible value, this information did not always allow predictions to be made regarding the impact of any food or combination of foods on the intact organism. Such information could only be obtained through biological experimentation, preferably in animals at different stages of growth and development." To this important conclusion might be added the further comment that before deductions are made about the applicability to man of

conclusions drawn from rat studies, direct studies should be made on man. The difficulties visualized by Gilbert and Gillman have been foreseen and overcome in most modern work on supplementation and enrichment as applied to man. In studies in our own department on the supplementation and enrichment of maize and wheat, we have taken care to see that there could be no possibility of deficiency of other nutrients. Full vitamin supplements and often salt supplements as well have been used.^{166, 409, 410, 411, 412} Admittedly there remains the possibility of excess or imbalance of mineral or vitamin nutrients by the technique used. This possibility is difficult to eliminate under the conditions of human feeding experiments and for the time being it must be kept in mind as a possible reservation to be applied to interpretations drawn.

As a result of the new attitude to protein malnutrition and in the light of population trends (Ch. 16) it is likely that there may be a world shortage of protein-rich foodstuffs in the next few decades. It will be necessary, therefore, to supplement or enrich cereals and other staples with small quantities of animal protein. These quantities will be smaller than the developed world is accustomed to, but larger than those at present available to the population of the underdeveloped world. Supplementary sources of good quality protein will be at a premium. The future of leaf protein* as a direct source of human food is therefore of great importance.³¹⁷ Because of the importance of these issues, a valuable chapter has been included by Platt, Miller and Payne (Ch. 28) on *The Protein Values of Human Foods*. Like Ch. 33 from the United Nations Agencies WHO and FAO, the detail may be of greater interest to nutritional scientists and public health administrators than to clinicians. The author nevertheless welcomes these chapters because of their fundamental importance in the background of clinical application. Contribution of the UNO agencies in this field in the last decade may prove to be of the greatest historical importance. The approach in Ch. 28 to a new method of estimating the nutritive value of protein in human mixed foods may well be another fundamental contribution to human nutritional science.

At the time of writing the whole subject of vegetable mixtures³⁶⁰ and of supplementation and enrichment of staple starch foodstuffs is due for examination by an international group.³²⁵ The conference

*This discussion does not include consideration of an equally important principle, namely the extent to which herbivorous animals can digest leaf and other proteins not suitable for human consumption and so contribute to man's protein intake through their flesh or products.

will be based on practical experience arranged during the last 2-3 years under a programme described in the Report of the Fifth Session of the Joint FAO/WHO Expert Committee on Nutrition.²¹⁸ A report on the findings of this conference will be included in an appendix chapter to this book. In the meantime, a valuable report on the subject has been compiled, with special reference to the pioneer activities of the INCAP group under Scrimshaw in Guatemala.^{20, 359}

Enrichment of maize with various natural foods has been reported from Eastern Europe and from South Africa.^{409, 410, 412, 413}

In a communication to the Washington Conference, Hansen has made a thoughtful contribution, based on nitrogen balance techniques on children, carried out in our Department. He draws attention to the great importance of defining the quantitative level of feeding before drawing conclusions about quality or nutritive value. For example, he finds that "at protein intakes less than 2.5 g./kg./day the nitrogen retentions achieved by supplementation of maize with lysine or tryptophan, and with pea flour, were significantly less than that achieved with a milk diet. These differences disappeared with higher intakes of protein." His work confirms the conclusion of the Committee on Amino-Acids of the National Research Council⁷⁹ that in animal work if the biological value of a protein is 60 or more, specific amino-acid supplementation is unnecessary providing there is a sufficiently high intake of protein. It seems, nevertheless, desirable to produce protein mixtures with biological values of 70 or more to ensure adequate protein nutrition under all environmental conditions.

Of very great practical value, is Hansen's conclusion that a maize/pea/mixture, supplemented with milk (18 per cent) or with fish flour (10 per cent) resulted in nitrogen retentions comparable to those of a milk diet at all levels of protein intake. Nitrogen balance, of course, does not give the full picture of nutritive value and the conclusions should be checked against growth and other criteria in human beings. An attempt has been made in this department to make such a check by means of two controlled feeding experiments in a local orphanage. One of these pilot experiments has been published⁴¹² and the other is in the press.²⁴⁴ The two were summarized and discussed at the Conference in Washington, D.C.³²⁵ Certain parts of the summary are repeated here:

"The first objective was to ascertain whether it was possible to achieve the degree of control which was necessary for a

scientific experiment. The second objective was to ascertain whether in a reasonably short time it was possible to demonstrate differences in the effects of control and experimental diets which could be exactly measured and statistically significant. The experimental and control groups for the first four to six weeks were selected by matching the children in pairs in respect of age, height, weight and general clinical condition. An additional internal control was applied by reversing the experimental and control groups for a further period of 4 – 6 weeks.

The experiments proved to give surprisingly quick and definite results. This may well have been a result of the poor state of nutrition of the children in both groups at the start of the experiment. The most measurable criteria proved to be mean group weights and mean group serum albumins. By grouping these two measurements for each of the 12 or more children respectively in the control and experimental groups differences came to have statistical significance for the group which would have been negligible for the individual. In both experiments, which were carried out in the winter, the super-vention of epidemic disease in the institution submitted the children to stresses which undoubtedly accelerated and emphasized the differences in nutritive value of the two diets under comparison. A full vitamin supplement was provided to both groups with the object of concentrating the interpretation of differences upon the quality of protein used as a supplement.

These experiments have brought out the fundamental importance of the amount of food consumed when the nutritive value of the protein is low or borderline.¹⁶⁸ It is now apparent that a diet of poorer nutritive value in respect of protein can give reasonably good results provided it is consumed at a sufficiently high level of nitrogen intake. When the level of nitrogen intake is limited, differences in nutritive value are greatly enhanced in their effects. When the nitrogen content of a staple food is very low it is not possible for a child to consume the necessary quantity for minimum protein requirements.

This would seem to give the clue to the real nature of pot belly in infants and young children among communities subsisting on diets which lead to protein malnutrition. In order to achieve the nitrogen intake which its system demands, a child is forced, on low-protein staple foods, to consume a quantity which distends its intestine. This effect is aggravated by the poor digestibility of most cereal diets."

These pilot experiments and the remarks quoted above (Gilbert and Gillman) on "predictions to be made regarding the impact of any food or combination of food on the intact organism" emphasize that we have not yet achieved any satisfactory definition of *nutritive value of a dietary protein* in spite of the comments made by the FAO Committee on Protein Requirements.¹²⁶ There are so many variables such as the balance of amino-acids in the protein, the other nutrients contained in the protein-rich foodstuff, the nutrient composition of the remainder of the diet, the level of activity, the ambient climate, the state of the intestinal bacterial flora, the presence of internal or external parasites, infective and metabolic disease, and the stresses and strains to which the organism is submitted, that conclusions on *nutritive value* must be drawn only for a particular dietary and other environmental context. This subject is discussed in detail by Platt (Ch. 28). His views are timely because of growing world population (Ch. 16) and the possible future of leaf protein as human food.^{360, 317}

More controversial than enrichment of staples with natural foods is their enrichment and supplementation with synthetic amino-acids. There is a large literature on enrichment with lysine which is the most-limiting amino-acid in most cereals.^{6, 129} A recent study³²⁹ sets the beneficial effects of lysine enrichment of a diet in which 95 per cent protein came from bread on a controlled and quantitative basis. We have had similar improvement of nitrogen balance in infants and young children,^{244, 409} as has Scrimshaw's group.³⁶ The rapid growth of industrial amino-acids must bring this subject to attention increasingly in the future.

CHAPTER 8

DIETARY FATS

DURING the last decade human nutritionists have "discovered" that there are "fats" rather than "fat" in the diet. To the biochemist and the experimental physiologist this may appear to be "another glimpse of the obvious" but even they have been very obtuse in this matter. In 1926 Evans and Burr¹²¹ made a primary observation on deficiency symptoms in the rat resulting from rigid exclusion of fat from the diet, and in 1929 and 1930 Burr and Burr⁶⁰ identified the deficiency as residing in certain polyunsaturated fatty acids.

The first real application of this work to the human started with the work of A. E. Hansen and his colleagues of Galveston, Texas, on the role of essential fatty acid (E.F.A.) in infant feeding. In their first publication in 1944 they found in a three-week-old boy with chylous ascites an unusual opportunity to study the clinical and metabolic effects of prolonged use of a diet extremely low in fat.¹⁶⁵ In many publications since then, they have defined a syndrome in infants on a diet based on skimmed milk and extremely low in fat and linoleic acid, but otherwise thought to be nutritionally adequate. This syndrome includes frequent large stools, perianal irritation, and dryness, thickening and desquamation of the skin. In a recent publication they report as follows: "The serum of all the infants on the low fat diet had extremely low values for the di- and tetraenoic acids and high values for trienoic acid which values changed with the addition of linoleic acid to the diet. The dienoic acid values reflected the dietary intake most markedly. Arachidonic acid administration did not change the dienoic acid level. It is concluded that young infants require linoleic acid in their diet."¹⁶⁴

In the applied biochemistry of E.F.A. deficiency a pattern of fatty acids in the serum has been defined which appears to be a result of deficiency of E.F.A.¹⁹⁴ This is dealt with in Ch. 19 by Bronte-Stewart. We have been interested in this pattern in a different context. Until very recently the standard treatment of kwashiorkor for the first few weeks was on skimmed milk. It was thought for a time that the disturbed structure, function and enzyme production of the gastrointestinal tract in kwashiorkor was such that the infant could not tolerate fat until cure had been initiated. Recent work suggests that

the infant may be better able to tolerate fat than had been assumed,⁹⁷ but we have continued to use a skimmed milk formula as our reference formula in experimental work designed towards elucidating the curative factors in skimmed milk. Among our cases treated on skimmed milk and on artificial amino-acid formulæ, we have seen develop in the serum, a fatty acid pattern very suggestive of E.F.A. deficiency.^{344, 345} It might reasonably be postulated that on the low-fat intake which is usually characteristic of the starchy diets which lead to protein malnutrition and kwashiorkor, reserves of E.F.A. might be small. With the very rapid metabolic turnover induced by treatment, an actual state of E.F.A. deficiency might develop before fat was reintroduced into the diet at the end of the period of initiation of cure. This postulate has still to be put to the test of experiment.

Apart from E.F.A. deficiency a revolutionary new concept of excess and/or imbalance of fatty acids arising from trends in the quantity and quality of fat in the diet of privileged groups and populations has been developed. This concept has focused itself upon the epidemiology of ischæmic heart disease, although it has possible applications to many other fields of medicine. The medical literature of the last five years is so filled with publications in this field that it is very difficult to make any adequate review, especially when controversial concepts are being modified every month. Recent reviews include a symposium on dietary fat, cholesterol metabolism and coronary disease from our own group³⁸⁹ and a special chapter in this book by Bronte-Stewart. The great activity in this field is recognized by the founding of a new journal, *The Journal of Lipid Research*, 1959 (Memphis, Tenn.), and a number of reviews on human lipid metabolism in general.^{388, 392, 394}

A special supplement of *Acta Medica Scandinavica* by Wygand⁴⁵⁸ reviews more recent work on the production of hypercholesterolaemia and atherosclerosis in rabbits by feeding different fats. This takes us back to the pioneer work of Anitschkow in 1933⁸ and comes from one of the departments which at the beginning of the present decade drew attention to the fall in death rate from circulatory disease during 1939-45 in the Scandinavian countries, with subsequent return to original values within a few years of the closing of the war. These mortality trends were related by the authors to the consumption of milk, butter, cheese and eggs. This suggestion led to the well-known epidemiological studies of Keys (Ch. 19).

Whatever may or may not be the implications of the many studies of the last decade in this field to the problem of ischæmic heart

disease and of atherosclerosis in general, we have learnt a great deal about the metabolism of lipids and the effect of changes in quantity and quality of dietary fat on the various lipid fractions of the serum and body tissues.

There can at this stage be no doubt that the level of total serum cholesterol and of some other lipid fractions can be lowered by altering the quantity and/or quality of dietary fat. The percentage of calories drawn from fat varies from 10 to 15 per cent among Japanese and mainly vegetarian groups to 35 to 45 per cent among privileged Western communities.

In the face of the last decade of work on dietary fat and serum lipids, recommendations have been made that the upper limit of dietary fat calories should be 30 per cent.²⁹³ Figures lower than 20 per cent are probably uneconomic in that they necessitate so large a contribution to calories from carbohydrates that the bulk of the diet becomes uncomfortably large. This latter effect is probably an important cause of pot-belly which is so widespread in underprivileged infants and young children in communities deriving their calories principally from cereals. Apart from their content of the fat-soluble vitamins, fats are important items in the diet for palatability and for reduction of bulk.

Far more important, however, than the quantity of fat is its quality. In general, fats of vegetable and marine origin tend to reduce serum cholesterol, while those of animal origin and those which have been saturated by hydrogenation processes tend to raise serum cholesterol. Other fats represented by olive oil are neutral in their effect. The recognition by Bronte-Stewart of this Department of the role of marine oils and of hydrogenation processes, is referred to by Jolliffe in the following terms: "Although all major discoveries have their foundations in the more distant past (and this one is not an exception), the immediate break-through was started by Kinsell *et al.* in 1952, who showed that the ingestion of certain different vegetable oils under the rigidly controlled conditions of a metabolism ward was followed by a major fall in plasma cholesterol and phospholipid levels. This finding was soon confirmed by several laboratories, but not all vegetable oils possessed this cholesterol lowering property and not all animal fats and oils raised cholesterol. At this point Bronte-Stewart, Antonis, Eales and Brock clearly showed that certain marine and vegetable oils which, in their natural state, lowered the elevated serum cholesterol level in man, after hydrogenation acted to elevate it just as do certain naturally occurring highly saturated fats, e.g. those derived from coconuts

and cow's milk. This discovery, now confirmed in other laboratories, has clearly proved to be of fundamental importance, like the finding of an important piece in a complicated jigsaw puzzle." This comment reflects the views of those who believe that the degree of saturation or unsaturation is the important determinant of the effect of a dietary fat on serum cholesterol.

Ahrens⁵ has particularly been an exponent of this view. In criticizing the essential fatty acid (E.F.A.) hypothesis^{237, 367} he makes three points:

- (1) that their definition of E.F.A. is ambiguous in relation to man;
- (2) that the only chemical structural feature which is common to the oils which reduce serum cholesterol levels in man is polyunsaturation; and
- (3) that his group find corn oil (rich in E.F.A.) and menhaden oil (almost devoid of E.F.A.) equally efficacious in reducing human serum cholesterol levels.

Yet there are many other qualities of dietary fats which may be important in this context. Such qualities as chain length, conjugated double bonds, and presence of trans acids are under investigation in our own and other laboratories. Ahrens recognizes that there is need to investigate the effects of these qualities. The absorption and metabolism of fats of different chain lengths has recently been investigated in rats. They were absorbed and respired in the breath at rates inversely proportional to their chain length.²²⁹ They also have differing effects on fat deposition in rats.²³⁹

The more unsaturated oils such as sunflower and corn oil will maintain levels of serum cholesterol at lower figures than in the control period for the great majority of individuals for as long a period as the oil is administered in doses of from 50 to 100 g. daily even though the total fat intake is high.¹⁵⁴

Many factors in the environment including other components of the diet undoubtedly influence the level of serum cholesterol.¹⁵³ It is also under nervous control.^{13, 439} Among the environmental factors which affect serum cholesterol certain endocrine abnormalities are important.¹⁵³ Undoubtedly female sex hormones have a lowering effect in keeping with the fact that mean serum cholesterol levels rise in females after the menopause and by the age of 70 equal male levels.

There are doubtless important genetic variables in controlling the level of serum cholesterol. It could well be that essential hypercholesterolaemia represents the homozygous expression of a gene or

genes which in heterozygous form produce the higher levels of serum cholesterol in so-called normal people. It is unlikely, however, that communities such as the Bantu are protected by absence of such a gene even in heterozygous form, for even in ~~them~~ the serum cholesterol can be driven up by unwise consumption of dietary fat. On the other hand, even cases of essential hypercholesterolaemia sustain an effective reduction in serum cholesterol levels when fed an appropriate quantity and quality of fat.²⁶⁵

All these genetic, endocrine, nervous and environmental influences on lipid metabolism must be taken into due regard. If, however, attempts are being made to reduce serum cholesterol, their importance is negligible compared with the quantity and quality of dietary fat.

The mechanism by which certain dietary fats lower serum cholesterol is very interesting but still quite obscure.¹⁵⁵ Gordon *et al.* have produced evidence that some unsaturated oils in a dose of 100 g. daily increase the excretion of bile acids—breakdown products of cholesterol—by up to 100 per cent while the serum cholesterol level falls. The absence of change in stool weight and stool fat content indicates that this action is not simply through laxation. Similar increases in bile acid excretion have been found in bile fistula.²⁵¹ This could suggest that feeding these oils increases the rate of elimination of cholesterol and its breakdown products. On the other hand, the mechanisms must be regarded as complex and *sub judice*.¹² The colonic bacteria may play an important part as is suggested by the observation of Goldsmith *et al.*¹⁵⁰ who reported greater increases from neomycin than from unsaturated oils.

Serum total cholesterol has been used in the foregoing discussion because it is the most convenient and reliable indicator of the effect of quantity and quality of dietary fat on serum lipid levels.¹⁴⁸ Nevertheless, other lipid fractions may be as important in relation to atherogenesis and thrombogenesis (Ch. 19).

It has been known for a long time that the quality of dietary fat affects the texture of subcutaneous fat in slaughter animals and in poultry eggs. Hirsch *et al.*¹⁸⁹ have demonstrated in man the ultra-short and short-term effects of different fats on various lipids in the serum and liver and the long-term effects on depot fat. Human beings fed corn oil for periods of from 6 – 9 months come to have a depot fat composition very similar to that of corn oil. It is difficult to imagine that such profound changes should not affect body metabolism in far-reaching ways, either during the period of deposition or during the period of mobilization of depot fat.

The potential relevance of these new discoveries in lipid metabolism to a great variety of diseases in which fat metabolism is obviously deranged is quite apparent. In no disease should it be more important than in the case of diabetes mellitus. It is surprising, therefore, how long it has taken hospitals to revise their diabetic diets which have contained 45 per cent or more of calories from fat. No one would seriously question the value of reducing these levels in diabetic subjects, nor the applicability of the same principles to disturbances such as essential xanthomatosis and essential hyperlipæmia.

The relevance to ischæmic heart disease and to the general problem of atherogenesis has, however, quite understandably stolen the scene. This is quite understandable because it was the Scandinavian experience of ischæmic heart disease during and after the Second World War and the consecutive epidemiological studies of Ancel Keys throughout the world which led to the real awakening of interest in lipid metabolism. This is not the book in which to review the relevance of dietary fat to atheroma. The views of our own group have been set down in detail in the symposium, "Dietary fat, cholesterol metabolism and coronary disease".³⁸⁹ The general problem can, however, be succinctly stated in the context of the present discussion.

There seems little doubt that there has been a very striking increase in the experience of myocardial infarction during the last two or three decades among privileged Western communities. This has not occurred to the same extent in the less privileged as in the more privileged social groups in these communities. The experience of underprivileged nations represented by the Bantu of southern Africa, is even better than among underprivileged Western groups. Several studies have shown that when underdeveloped communities are exposed to the pattern of Western civilization for a decade or two, they begin to experience myocardial infarction as a health problem. These epidemiological changes in myocardial infarction correlate well with mean levels of total serum cholesterol among the at-risk group, that is males between the age of 40 and 50 years, and it has been shown in the preceding discussion that mean serum cholesterol levels correlate with the quantity and quality of fat consumed in the diet. What could be more reasonable to hypothesize therefore that privileged Western civilization is leading to an increase in the prevalence of myocardial infarction by raising the level of total serum lipid and altering the distribution of lipid fractions in serum and tissues in such a way that atherogenesis is

encouraged. The rising prevalence of myocardial infarction in various groups correlates, of course, also with many other variables common to Western privileged civilization. The use of telephones and motor cars is often quoted by those who deny the importance of dietary fat. The counter argument is, of course, that epidemiological studies do no more than suggest clues which have to be investigated. The dietary fat clue has been investigated and perfectly reasonable theories have been put forward which would explain the mechanisms through which dietary fat operates. No such mechanism has yet been postulated for the use of telephones and motor cars, although it is easy to postulate that the former causes emotional strain and the latter reduces exercise.

At this point it is reasonable to put forward a hypothesis to explain the great increase in prevalence in myocardial infarction in certain communities in the last decade. Myocardial infarction is undoubtedly a disease of multiple ætiology. Its essential basis is the development of atheroma in the coronary arteries. This by itself is not enough to cause myocardial infarction if Morris²⁸⁶ is right in his view that there has been a decrease or at least no increase in the distribution or severity of atheroma in the coronary arteries of the population of the eastern districts of London during the last three decades, during which time there has been a great increase in experience of myocardial infarction. It is therefore necessary to postulate that some other factor determines the coagulation of blood in the atherosclerotic coronary arteries. Let us call this process occlusive thrombogenesis. There is certainly abundant evidence, both in experimental work and in epidemiological studies, that serum lipids and tissue lipids, which we have shown are controlled by dietary fat intake are intimately related to the processes of atherogenesis and indirect evidence that serum lipids may be related to occlusive thrombogenesis. This matter is more fully reviewed in Ch. 19. However important dietary fat may be in the processes of atherogenesis and occlusive thrombogenesis, this is quite obviously not the whole story of ischæmic heart disease. It is quite clear that genetic factors operate; perhaps through the anatomy and histology of the coronary arteries; perhaps through liability to hypertension, which always aggravates atherosclerosis; perhaps through anomalies of lipid metabolism; or perhaps through the many factors which control intravascular thrombosis. Endocrine factors are undoubtedly important, as is evidenced by the close association between hypothyroidism and serum cholesterol. Similar endocrine influences through the gonads undoubtedly account for the relative freedom of

pre-menopausal women from myocardial infarction. Environmental factors other than diet which seem to be reasonably relevant include lack of exercise, tension and strain of high pressure living, and cigarette smoking. Exercise may protect by developing collateral circulation as coronary arteries become progressively obliterated. Cigarette smoking may affect the neuromuscular control of the coronary artery walls with consequent narrowing. It may also affect the complex mechanisms controlling intravascular thrombosis and fibrinolysis. There is some evidence that psychic and emotional states may also affect the latter mechanisms.

This discussion of myocardial infarction and ischaemic heart disease is written against the context of diet. To return to diet, we can say that while admitting the many variables which may affect the prevalence of I.H.D. none is more obviously relevant and more easily controlled than the quality and quantity of fat in the diet.^{41, 47} This statement does not deny that other dietary differences may be important. The diets consumed by those communities which have a high prevalence of I.H.D. differ from the diets of those communities which have a low prevalence of I.H.D. in many ways. Whatever may be the final solution of this matter, the research has been highly interesting and educative.

The possible relevance of this research to the modern epidemic of ischaemic heart disease is discussed briefly by Pickering³¹⁶ who, while admitting that dietary manipulations can lower the serum cholesterol level, rightly counsels caution in assuming that such manipulations represent a rational and potentially effective line of treatment in ischaemic heart disease. The note of caution is justified since the possible effectiveness of dietary manipulation in the prevention of recurrences of myocardial infarction has swept the world and led to many new books on diet, as well as to a challenge to those who produce and process dietary fats.

In diseases such as hypothyroidism and diabetes where serum cholesterol is always raised, widespread and premature atheroma and atherosclerosis is the rule. This correlates in most of these diseases with early and high prevalence of myocardial infarction. The principles that underlie the epidemiology and pathogenesis of myocardial infarction are therefore relevant to the total problem of atheroma and atherosclerosis. These vascular changes in the coronary, cerebral and renal systems are intimately linked with hypertension, another constitutional disease in which diet may well play a part. Hypertension aggravates the effects of coronary and cerebral narrowing; in the first case through myocardial hypertrophy making

a greater demand upon coronary blood flow, in the latter case by weakening cerebral arteries which have to resist a higher pressure with little or no outside support. Renal atheroma is both a cause and a result of hypertension. In view of these complex inter-relationships it is not surprising to find that the distribution of I.H.D. in geographical pathology and intercommunity and inter-racial studies does not correlate closely with cerebral vascular disease, hypertension and renal disease. Brock and Bronte-Stewart⁵¹ gathered together evidence to show that although the Bantu of southern Africa were so remarkably free from ischæmic heart disease, they were by no means favourably placed in respect of hypertension, cerebral vascular disease and renal disease. Similar observations have recently been reviewed by Dahl⁸⁷ in respect of the Japanese people. Here then are a group of diseases, all of them of multiple, complex and degenerative ætiology, which appear in different communities with differing severity of emphasis. In all of these there is evidence that among the many environmental causes, different patterns of diet may initiate and slowly condition the constitution towards a degenerative termination.

Local interest in the relation of dietary fat, serum cholesterol and ischæmic heart disease arose from the remarkable freedom of the Bantu of southern Africa from I.H.D.⁵³ although not from hypertension and cerebro-vascular atheroma. The Bantu are in this respect comparable with the Japanese, in spite of the very great differences in stage of development and dietary habit and form a striking contrast with South African Whites who have almost as high a prevalence as any other race in the world. The freedom of the Bantu from I.H.D. was recently questioned by Laurie and Woods in the cliché "there is as much atheroma in the Bantu as in Barts". This claim was repudiated at the stage of its preliminary announcement.⁵³ The publication of the fuller data²⁴⁶ has not led to any further conviction. Obviously they have failed to appreciate the nature of *endemic cardiopathy of unknown origin* (Chs. 13 and 30).

In Ch. 19 Bronte-Stewart has reviewed the problems of dietary fats against the background of his own very significant contribution to research in this field.

In Ch. 31 on Recent Trends in Nutrition in the French language, Trémolières presents some interesting evidence on the subjects discussed above. He finds that a high lipid, high protein diet produces atheroma and arteriosclerosis in rats irrespective of whether the serum cholesterol is or is not raised by a supplement of 2 per cent cholesterol in the diet. He quotes Jacquot *et al.* as concluding from

comparison of rats on lard with rats on sunflower or poppy seed oil, that reserve or depot fats rich in E.F.A. are less mobilizable than those rich in saturated fatty acids. Trémolières concludes that high-protein feeding is also important in the production of arteriosclerosis. His chapter also includes evidence that linolenic acid is not an essential fatty acid, that pyridoxine protects against E.F.A. deficiency in rats and that silica protects against atheroma in the rabbit.

Gas Chromatography. The introduction of gas chromatography has enormously accelerated the previously tedious analytical methods for determining the fatty acid pattern of various lipid fractions in food, serum and body tissues.¹²⁸ Many reports are appearing on studies in this field. Bottcher *et al.*³² report on the analysis of lipids from young undiseased human aortas and from aortas in three defined stages of atherosclerosis. The lipids were separated into phospholipids, free fatty acids (F.F.A.), cholesterol esters (C.E.) and glycerides plus free sterols, and the fatty acids obtained from these four fractions were analysed by gas chromatography. The most striking changes were observed in cholesterol-ester fatty acids (C.E.F.A.) in which with increasing atherosclerosis of the artery the polyunsaturated acid percentage rises from 29 to 46 per cent and the saturated acids decrease from 31 to 17 per cent.

The short-term changes in lipids of serum and liver and longer-term changes in depot fat described by Hirsch¹⁸⁹ under the influence of various qualities of dietary fat might reasonably be expected to be reflected in differences between people on widely differing diets. Comparison of Whites and Bantu in southern Africa might show marked differences which could be correlated with the respectively high and low prevalence of ischaemic heart disease in these groups.⁵⁸ Bronte-Stewart *et al.* have made preliminary studies in this way. It is too early to give definite results but certain trends are apparent: The preliminary analysis shows fewer and smaller differences between Whites and Bantu than might have been expected considering the very different dietary background of the two groups.

CHAPTER 9

CARBOHYDRATES, VITAMINS, TRACE AND OTHER MINERAL ELEMENTS

CARBOHYDRATES

CARBOHYDRATES would appear to be the cinderella of human nutrition studies at present. There is still very little applied knowledge of the fate of their varieties in human metabolism. The usual information in textbooks about poly-, tri- and di-saccharides and hexose and pentose sugars seems to have little practical application in the present state of knowledge. An exception to this statement is the use of fructose as a substitute for glucose under certain conditions of metabolism. Fructose is taken up more readily by the liver and its metabolic pathways are less disturbed by ether anaesthesia than is the case with glucose.¹⁰⁸ It may be used as an alternative to glucose in the early stages of treatment of diabetic ketosis when its different metabolic pathway gives it a positive value. It is capable of relieving some of the symptoms of hypoglycaemia³⁶² and is apparently capable of substituting in part for glucose in brain and heart.⁸⁸ It would not be surprising if, during the 1960s, there were a forward advance in this field.

VITAMINS

The rather detailed consideration of proteins and fats in Chs. 7 and 8 is in line with remarks in the introduction about their comparative neglect in nutrition literature in the past and the great interest which their study has evoked in the 1950s. In the same section of the introduction it was implied that vitamins had occupied the centre of the stage for so long that they could now be allowed to retreat to the back of the stage for a period of time. In line with this attitude they will be given rather cavalier treatment in this monograph.

Recent advances in vitaminology are thoroughly reviewed in two recent general textbooks on nutrition. The second edition of Wohl and Goodhart⁴⁴⁷ devotes 113 pages to the subject under 15 headings. The chapter on vitamins in the first edition of Davidson, Meiklejohn and Passmore⁹⁰ occupies 65 pages and considers them under the headings *Fat Soluble* and *Water Soluble*. The latter chapter starts with the following remarks: "The vitamins are organic substances

which the body requires in small amounts for its metabolism, yet cannot make for itself (at least in sufficient quantity) from proteins, carbohydrates or fats. For the most part, they are not related chemically and differ in their physiological actions. They are classified together because the same general laboratory procedures led to their discovery and isolation."

In this monograph some vitamins, such as B₁₂ and folic acid, are discussed together with some minor (trace) elements as *haematinic nutrients* (Ch. 13). In Ch. 25, vitamin D is discussed in relation to the skeleton and calcium metabolism. In Ch. 13, thiamine is discussed particularly in its relationship to myocardial metabolism.

This cavalier treatment of the vitamins should not be interpreted as indicating any lack of respect for them or for their extremely useful and vital functions in the human economy. It implies merely a wish to allow other branches of nutritional science to catch up on existing knowledge of vitamins in order that the functions of the latter may be more fully understood in their application to man and his health. It seems clear, for example, that our understanding of B complex vitamins must be delayed until there has been further elucidation of the role of amino-acids and proteins in nutrition, since the functions of this group of vitamins are so intimately related to protein metabolism. It is likely also that there will be a forward advance in our understanding of the fat soluble vitamins when we know more about the metabolism of the fats. By the same token the present neglect of carbohydrates, the cinderella of human nutritional science must be corrected if we are to have a proper understanding of the functions of certain other vitamins.

Finally, the comparative neglect of vitamins in this monograph should be interpreted as indicating a hope that the era of therapeutic vitamin quackery in clinical practice has come to an end.

Vitamin A

The mammalian form of this fat-soluble vitamin is an alcohol (C₂₀H₂₉OH) and is known as A₁. The absorption spectrum of vitamin A has an intense band in the ultra-violet region at 238mμ. This property forms the basis for accurate estimation. The other method for estimation is based on the fact that solutions of vitamin A in antimony trichloride produce an intense blue colour. The stability is fairly good towards heat but it is easily oxidized. Its provitamins are a group of carotene and carotenoid pigments occurring as yellow and orange pigments in fruit and vegetables. Conversion of provitamins to vitamin A₁ takes place in mammals in the intestine and

to some extent in the liver which, in the well-fed human, stores reserves sufficient for 6–9 months.

Visual Purple. The eye remains the most sensitive indicator of human deficiency of vitamin A, but its specificity and degree of sensitiveness is still a problem. This is probably inherent in the very large reserves of this vitamin stored in the liver. Their size makes it difficult to deplete them under controlled conditions. Secondly, there are very marked differences in visual adaptation between apparently healthy people which may be more closely related to genetic factors than to environmental factors including nutrition.

There have been some advances in the physiological chemistry of visual purple metabolism which illustrate the complexity of the mechanisms involved. In the rods of the retina vitamin A is converted by enzymes to retinaldehyde. This combines with opsin to form rhodopsin (visual purple). When exposed to light the link between retinaldehyde and opsin is broken. This mechanism has been complicated by the discovery by Hubbard and Wald²⁰³ that in the rhodopsin cycle the bleaching of rhodopsin yields all-trans retinene which must undergo isomerization before it can regenerate the visual pigment. Alternatively, having been reduced to all-trans vitamin A the latter must also undergo isomerization before it can take part again in rhodopsin synthesis. So that, not only does the vitamin undergo oxidation and reduction but also cis-trans isomerism. In 1944²⁸⁷ retinene was shown to be the same as vitamin A aldehyde.

Ocular Effects and Requirement. Deficiency of vitamin A results in nightblindness (*hemeralopia*), on the one hand, and xerophthalmia and keratomalacia on the other. Both may occur simultaneously, but should be regarded as distinct, for the one is the result of deficiency in the specialized structure of the retina and the other the result of deficiency in epithelial cells which may also be manifested by hyperkeratosis of the skin. Before developing the full picture of xerophthalmia the patient may show Bitot's spots which are triangular specks under the conjunctiva at the corners of the eye. During the Second World War, Hume and Krebs²⁰⁴ studied the effects of vitamin A deficiency in the human adult. After 10–20 months of deficiency only 3 of the 16 subjects showed any change in their dark adaptation. In one man, the sensitivity of the fully dark adapted eye fell to 1/10th, while in another it fell to 1/100th of the initial value and yet they thought that their night vision was only slightly impaired. All the subjects showed constriction of the visual fields of the fully dark adapted eye 10 months after starting

on the diet; 2,500 International Units of vitamin A would restore the plasma vitamin A level to normal and the dark adaptation curves were also restored to normal. In the Sheffield Experiment, there was a fall in the blood vitamin A level from about 120 International Units per 100 ml. of plasma to 50 International Units per 100 ml. of plasma before there was any detectable change in dark adaptation. The conclusions drawn from these human experiments were:

- (1) That it is very difficult to produce vitamin A deficiency in a well-fed European adult.
- (2) The sensitivity of the eye to light can fall to about 1 per cent of the normal without the subject being seriously nightblind.
- (3) Cure is achieved by relatively small doses of vitamin A.

Many more lesions are known to occur in animals. In the rat, severe maternal vitamin A deficiency causes retinal and other ocular malformations in the young.⁴²⁸ Calves²⁸⁴ and rabbits²⁷⁴ with vitamin A deficiency may go blind owing to abnormal growth of bone surrounding the optic foramen. Wolbach and Howe⁴⁵⁰ showed in 1925 that epithelial cells undergo squamous metaplasia in vitamin A deficiency. The consequent blocking of lachrymal glands and ducts and sebaceous glands play an important part in the production of ocular complications.

Dowling and Wald¹⁰⁵ have made a recent contribution to the old clinical and survey problem of relating night blindness to the overall picture of vitamin A deficiency. They suggest that many tissues including the rods of the retina contain structural proteins which are stabilized by combination with vitamin A or its derivative, and that these also deteriorate in the deficiency state. Wald⁴²³ has shown that vitamin A acid (which does not naturally occur in the body) is able to function as vitamin A for the extravisual functions of the vitamin and has shown that it can promote growth in vitamin A-deficient rats, but does not cure their defective dark adaptation.

Other Tissues. Our knowledge of the mode of action of vitamin A in the rest of the body is far less certain. Some of the lesions resulting from vitamin A deficiency are known in mammals including man. Changes take place in the epithelial cells of many tissues and it is possible that there is some interference with the formation of mucopolysaccharides.²⁸⁵ There is also experimental evidence that there is diminished production of glucocorticoid by the adrenal cortex in vitamin A-deficient rats.⁴⁵¹ There is histological evidence to support

this.²⁵⁴ In animals squamous metaplasia also occurs in the bronchial tree and, in dogs, in the urinary tract leading to calculi. In the skeleton, there is irregular development of the skull and vertebræ. Mellanby²⁷⁵ showed that nervous disorders could be produced in experimental animals if the diets contain too little vitamin A. The precise cause is still uncertain. In some it may be due to bony deformity and pressure of nerves, but Wollan and Millen⁴⁵³ have shown that there is also a rise in C.S.F. pressure which appears to be due to an increase in secretion rather than to osseous changes. No changes in bone structure have been attributed to vitamin A deficiency in man.

Vitamin A is related to the development of the teeth.²⁰⁹ The ameloblasts which form the enamel are epithelial cells. Experimentally vitamin A deficiency causes defective enamel formation in puppies, but this has not been shown to be a factor in man.

Therapeutic Uses. Vitamin A is absorbed more efficiently than carotene and is therefore preferable. In the absence of any defect in fat absorption it can be given by mouth.

For defective dark adaptation 1,250 International Units of vitamin A usually proved sufficient in depleted but otherwise healthy men. Ill patients may require high doses. Vitamin A is also used curatively for the other ocular results of its deficiency. It has been used in the treatment of a variety of skin diseases with very variable results.²⁴⁹ During the war very large doses of vitamin A were used in an attempt to improve the night vision of fighting men. It is very doubtful whether any significant improvement was achieved.²⁸⁵

Fat Absorption. The vitamin A tolerance test has been used as an index of fat absorption and is of use in the detection of steatorrhœa. Beaumont and Lemegre¹⁹ compared the vitamin A tolerance test in 54 anginal patients with controls and found abnormally high values with essential hyperlipæmia. They interpreted their data as indicating a group of different metabolic disorders which have in common, disturbance of lipid metabolism and coronary artery disease, and thought that the vitamin A tolerance test was a means of identifying those subjects who have a disturbance of the preliminary stages of lipid metabolism. There was no correlation with the serum cholesterol.

The INCAP group has used vitamin A also for the study of fat absorption in kwashiorkor. They found that there was defective vitamin A absorption in kwashiorkor and that this defect could be corrected by therapeutic amounts of acidified half-skimmed milk.

This effect was demonstrable as early as the fifth day of treatment and in some as early as the third day.¹⁰ The reason for the malabsorption of vitamin A in kwashiorkor is not clear. It may be related to defective secretion of pancreatic lipase. There is also evidence of poor vitamin E absorption in kwashiorkor.^{358, 407}

Effects of Excess. Since the recording of acute intoxication from consumption of the vitamin A-rich livers of polar bears the toxic effects of excess have been known. It causes drowsiness, headache, vomiting and extensive peeling of the skin. Rodahl and Moore³³³ showed that the polar bear liver may contain approximately 2,000,000 International Units of vitamin A/100 g.

Two types of lesions have been described; Marie and See²⁶⁷ have noted the development of bulging of the fontanelles and vomiting presumably due to increased secretion of the C.S.F. in young infants given single doses of about 300,000 International Units of vitamin A. Josephs²²³ has described precocious skeletal development with hepatomegaly, splenomegaly, anæmia, clubbing and coarse, sparse hair following chronic excess in a three-year-old boy. Most of these abnormalities were corrected and the vitamin A blood level returned to normal as soon as the excessive intake was stopped. Gerva *et al.*¹⁴¹ have described a 28-year-old woman who had been ill for eight years with headaches, coarse itching skin, visual disturbances and skeletal pain who was eventually found to have hypervitaminosis A due to continuous administration for ichthyosis. She was completely cured by stopping vitamin A. Hypercarotenosis follows excessive ingestion of carotene especially in the form of carrots. The skin, but not the conjunctiva, becomes yellow. Cohen⁷⁵ has shown that hypothyroidism increases the liability to carotene pigmentation.

Congenital Defects. Severe maternal vitamin A deficiency in the rat induces retinal and other ocular malformation in the young.⁴²⁸

In addition, a variety of congenital defects has been produced in rats by the administration of a single large dose of vitamin A on the 9th, 10th and 11th day of pregnancy.⁹⁹ The general subject of congenital malformation induced by maternal diet-deficiency was reviewed by Warkany in 1955.⁴²⁹

Roels *et al.*³³⁵ have studied avitaminosis A in Ruanda Urundi. They suggest that the addition of fats to the diet may contribute to the relief of vitamin A deficiency because they showed that the absorption of carotene was enhanced by the addition of 18 g. of olive oil per day. This study was made on subjects probably consuming low intakes of fat. A recent report from a Mediterranean area

suggests the possibility of a role of vitamin A deficiency in the production of goitre.¹⁹⁸

Vitamin B₁ (Aneurine; Thiamine)

The importance of this vitamin to the nervous and cardiovascular systems is well known. It would seem that thiamine as cocarboxylase takes part in the oxidation of alpha-keto acids and when it is deficient pyruvate accumulates, as does pyruvic aldehyde²⁴⁰ which is more toxic.²⁴⁵ Diets relatively high in carbohydrate but deficient in thiamine will increase the accumulation and this is particularly important in cells such as nerve cells which have a predominantly carbohydrate metabolism as well as in cardiac muscle cells which use pyruvate for metabolism. Thiamine is also required for the synthesis of acetylcholine and this may result in imperfect function of nerves. In man acute deficiency of thiamine results in the accumulation of pyruvate in the brain stem and probably causes vascular dilatation and minute hæmorrhage characteristic of Wernicke's encephalopathy, or if the heart bears the brunt acute cardiac beriberi results. Both respond dramatically to therapy with thiamine. Yudkin⁴⁶¹ points out that a diet which produces beriberi also tends to produce deficiency of protein, riboflavine and nicotinic acid. The rice diets responsible for the disease are always deficient in many vitamins besides thiamine.

Infantile beriberi occurs mainly in the Far East. It is seen in the first few months of life and the course is rapid. There is loss of appetite, vomiting, abdominal pain, restlessness followed by œdema tachycardia, dyspnoea and aphonia. This is due to laryngeal œdema and is responsible for the beriberi "cry". Death may occur in a few days from heart failure.

Adult beriberi in the classical "wet" variety presents with cardiac failure with warm extremities, dilated blood vessels, and mild hypertension. This has been referred to in Ch. 13.

Amongst British prisoners of war in the Far East de Wardener and Lennox¹⁰² described loss of appetite, vomiting and insomnia associated with nystagmus together with a variety of ocular palsies. Mental changes were prominent and coma and death ensued in the absence of treatment. They responded promptly to thiamine. This disease was very similar to Wernicke's encephalopathy due to reversible biochemical lesions in the corpora mammillaria resulting from thiamine deficiency and reversed by thiamine administration.

The blood thiamine content is not a practical procedure for establishing the diagnosis of thiamine deficiency. Urinary thiamine

content falls as soon as dietary intake of thiamine declines and so is of no value. Saturation tests have proved unsatisfactory. Blood lactic and pyruvic acid levels rise in vitamin B₁ deficiency. These are the most reliable biochemical guides and are brought out by doing the estimation after exercise and oral glucose. This biochemical abnormality must be reversed by therapeutic thiamine to make the diagnosis more certain.

In man parenteral administration is rarely necessary in treatment. 10 mg. by mouth are usually adequate and this dose is usually given three times daily in depleted subjects. The body content of thiamine in health is 25 mg. and if more than this is given it is merely lost in the urine. Not only are larger doses intramuscularly or intravenously unnecessary, but also they are potentially dangerous because in rare instances an anaphylactoid reaction may occur and at least two deaths have been recorded. Treatment with thiamine has its most dramatic results in wet beriberi, Wernicke's encephalopathy, and in infantile beriberi. With regard to dry beriberi (polyneuritis), Yudkin⁴⁶¹ has emphasized that improvement is slow and may never be complete if there is long-standing paralysis. He believes that it is worth persisting with treatment for many months. The acute polyneuritis associated with wet beriberi often improves well on therapy. There is no indication for the use of treatment with vitamin B₁ in a wide variety of other diseases where treatment with it has been tried, for example, trigeminal neuralgia, infectious polyneuritis, herpes zoster, heavy metal poisoning, ulcerative colitis, etc.

Nicotinic Acid

The practical implications of recent reports on the utilization of tryptophan as a precursor of nicotinic acid were emphasized by the National Research Council when it issued its recommended dietary allowances in 1958. It proposed that the term niacin-equivalent be substituted for niacin. Recent reviews^{149, 199} have described the experiments aimed at confirming the estimation that 60 mg. of tryptophan is the dietary equivalent of 1 mg. of nicotinic acid. The fact that some protein which is virtually devoid of niacin can supply all the niacin equivalents necessary for optimum health makes it necessary to have this estimation of the amount of tryptophan in the diet when one evaluates niacin requirements. It has been pointed out that the requirements for niacin equivalent is dependent upon total caloric intake, either as a function of metabolism plus work or of body size,¹⁴⁹ and accordingly one should think of the

requirements for niacin and tryptophan as being related to calorie consumption as one does for thiamine requirements.

(The amide of nicotinic acid, nicotinamide, is an important constituent of coenzyme 2 (triphosphopyridine nucleotide, T.P.N.) in human red blood cells, and also is a component part of the hydrogen acceptor diphosphopyridine nucleotide (D.P.N.) found in heart muscle and called coenzyme 1. Nicotinic acid is rapidly converted in the body to its amide nicotinamide.) The biological function of coenzymes 1 and 2 is either to donate or accept hydrogen ions in vital oxidation-reduction reactions. The conversion of lactic acid to pyruvic acid is typical of such a reaction some of which require D.P.N., others T.P.N. During this passage of hydrogen ions A.T.P. is synthesized by oxidative phosphorylation.

For the conversion of tryptophan to niacin three other vitamins are also necessary: pyridoxine, riboflavine and thiamin.²¹⁰

In the past there was a tendency to ascribe pellagra solely to a deficiency of nicotinic acid. It seems that the other two factors which were incriminated before the emphasis fell on niacin, i.e. maize and tryptophan are coming into their own again and it seems probable that all three play a part in its ætiology. As regards the specific effect of maize, it is possible that it contains a chemical analogue of nicotinamide which competes with it in metabolism. Chick⁶⁹ has recently reviewed this subject. It is of interest that oral administration of L-leucine increased the urinary excretion of N-methyl nicotinamide, in healthy subjects and in patients with pellagra.¹⁵² In addition, 20–30 g. daily caused a temporary deterioration in the mental state of patients with pellagra. This probably results from the amino-acid imbalance causing a depletion of nicotinic acid in the tissues which is of great importance in subjects on marginal diets.

(Nicotinic acid deficiency may result from poor dietary intake, from poor absorption or from disordered metabolism. At certain times the needs of the body may be increased, for example following surgical trauma, in pregnancy, lactation, rapid periods of growth, thyrotoxicosis. Under these circumstances normal dietary content might not be sufficient in the presence of previously subnormal content. Of great interest is the development of nicotinic acid deficiency secondary to metabolic disorders.)

- (1) The malignant carcinoid tumours may divert as much as 60 per cent of the body's tryptophan, in order to form large amounts of 5-hydroxytryptamine.³⁶⁸

- ✓(2) (The use of isoniazid in the treatment of tuberculosis may induce a deficiency of nicotinic acid. This is referred to again in the section on pyridoxine.)
- (3) Patients with the Hartnup Disease¹⁶ present with pellagra and attacks of cerebellar ataxia. The disease occurs in childhood, and unlike most other hereditary metabolic conditions tends to improve with age. The rash responds to nicotinamide therapy and the ataxia recovers spontaneously. So far only seven other similar cases to the Hartnup family have been described. One biochemical abnormality is a generalized amino-aciduria of renal origin owing to a failure of reabsorption of amino-acids from the glomerular filtrate. The plasma amino-acids are normal.

Blood levels of nicotinamide, D.P.N. and T.P.N., tend to be low in deficient patients, but the overlap of values between normal and deficient people is considerable. Loading tests and the urinary content of nicotinic acid and its derivatives have been disappointing in clinical use.

(Because nicotinic acid has a direct vasodilator action on blood vessels, nicotinamide is preferred for therapy. One should aim at giving the patient an adequate mixed diet which should be rich in all vitamins. About 500 mg. of nicotinamide should be given daily. If the patient is vomiting, 800 mg. a day can be given intravenously. Under certain conditions, large doses of tryptophan may be effective.)

While a macrocytic anæmia occurs in niacin deficiency in dogs,²⁹⁸ this has not been described in man, and the anæmia in human pellagra has been ascribed to a deficiency of folacin.²⁴² One case of anæmia, with giant stab forms responding to niacin, and not to iron, has been reported.¹³⁴

There have been numerous recent reports on the usefulness of nicotinic acid in reducing serum cholesterol.^{2, 192, 309, 310, 311} It has been shown that such falls in serum cholesterol are accompanied by an increase in basal metabolism in normal young adults.⁷ The mechanism by which cholesterol is lowered is not yet resolved. In some of these reports, enormous doses of nicotinic acid were used.¹³⁸ Experiments in rabbits have shown that large oral doses of nicotinic acid reduce the hypercholesterolaemia and the aortic atheromatosis produced by the administration of cholesterol.⁶⁶ Two to 5 g. of niacin per day for one week may cause no further decline in serum cholesterol, which had already been lowered by a low-fat diet.

Again, in one patient the serum cholesterol fell when he was given 3 g. of niacin, but fell sharply again when the low-fat diet was added. Buffered nicotinic acid 1 g. t.d.s. has produced the same fall in serum cholesterol as nicotinic acid itself without the undesirable side effects.¹⁹⁷

Pyridoxine (Vitamin B₆)

Pyridoxine acts mainly as a coenzyme in the decarboxylation and transamination of a number of amino-acids and therefore requirements of the vitamin are increased with a high-protein diet. When it is deficient deamination increases and urea production increases. Vitamin B₆ is essential for the breakdown of kynurenine into alanine and anthranilic acid, and if this does not occur kynurenine accumulates and is converted into xanthurenic acid which appears in large amounts in the urine. Kynurenine is derived from tryptophan. The urinary xanthurenic acid level is a useful test for vitamin B₆ deficiency. Vitamin B₆ also plays a part in the enzymes concerned with the interconversion of certain fatty acids and also in normal adrenocortical function.

Adults living on a pyridoxine-deficient diet for up to two months remained symptom-free.¹⁷⁷ However, if pyridoxine antagonist, desoxypyridoxine, is given concurrently within two weeks seborrhoea alike skin lesions occur around the eyes, nose and mouth, plus cheilosis, glossitis, weakness, dizziness and vomiting and a mild lymphocytopenia. These signs disappear within three days of giving pyridoxine. Peripheral neuritis may also occur, and the peripheral neuritis which develops when large doses of I.N.H. are used can be reversed by giving vitamin B₆.

In 1952 McConnell and Cheetham²⁵⁹ described the first case of pellagra in a patient on I.N.H. Earlier that year Pegum³¹⁴ had described the development of burning feet in another patient. Since then, more cases have occurred,^{222, 455} and it seems likely that I.N.H. competes in some ways with nicotinic acid.

It is known that I.N.H. has neurotoxic effects—peripheral neuritis, convulsions, optic atrophy and psychosis.¹¹⁶ There have been several reports of the development of peripheral neuritis in patients receiving I.N.H.^{183, 241, 331} The neuritis appears more commonly with high doses²²⁸ and there is also a higher incidence in the second or third course of I.N.H. An increased tendency to fits has been noted in epileptics on I.N.H.²⁷ Optic atrophy has occurred and there is a suggestion that it has improved on stopping I.N.H., but one has to bear in mind that tuberculous meningitis may cause

optic atrophy. There is good evidence that I.N.H. itself may cause optic atrophy particularly with intrathecal administration^{227, 231} Psychosis occurred in 4 of 173 patients in the M.R.C. trial.²⁷¹ Withdrawal of I.N.H. usually leads to a reversal of the psychosis. Investigations have shown that it is improbable that the bacteriocidal activity of I.N.H. can be explained by its action on transaminase or other enzymes requiring pyridoxal phosphate.⁴⁶⁰ Daily doses of 300–900 mg. of I.N.H. given in the treatment of tuberculosis caused an increased excretion of kynurenine and xanthurenic acid in tryptophan load tests.³²⁴ This has not been a universal finding.³⁴² However, the latter workers found lower levels of glutamic-oxalacetic transaminase in the blood of patients receiving the drug. It was soon shown that the neuritis could be relieved by giving pyridoxine and it protects animals against the toxic effects of I.N.H.⁴¹³ Pyridoxine is effective in the prevention and treatment of the neurotoxic effects of I.N.H.^{62, 227, 307} and does not diminish its chemotherapeutic action.^{413, 430} Jackson²¹¹ has stated that the best treatment for the neurological side effects of I.N.H. is systemic vitamin B complex and not a particular component of it.

The experimental production of vitamin B₆ deficiency in man and considerable animal experimentation have suggested that convulsions might be a critical manifestation of this deficiency in infancy. During 1953, convulsions and hyperirritability occurred in about 3 out of every 1,000 infants fed a proprietary formula with a decreased content of vitamin B₆. These symptoms disappeared after pyridoxine was given, or after a diet more adequate in pyridoxine was given. When the proprietary formula was supplemented with pyridoxine, the syndrome disappeared.^{25, 83, 280} This formula was deficient in B₆, and was fed to five infants resulting in convulsions which were prevented by giving supplementary vitamin B₆. Xanthurenic acid excretion was increased in the only one of these infants thoroughly studied.²⁵ A mother given large amounts of pyridoxine during her pregnancy was delivered of a child who developed seizures within 48 hours of stopping 2 mg. pyridoxine hydrochloride daily.²⁰⁶ It is suggested that this child was an example of induced pyridoxine dependency. The work of Bessey *et al.*²⁵ indicates that intakes of less than 0.1 mg. of vitamin B₆ per day are associated with the development of clinical manifestations in a significant number of infants. Intakes of 0.3 mg. per day or more have not been associated with these symptoms, nor with the increased excretion of xanthurenic acid following a tryptophan load test in normal infants. There have been two or three infants described in whom at least 2 mg. of

pyridoxine per day were required to prevent convulsions, and it seems that in these children there is a metabolic abnormality in the handling of pyridoxine by the body. It is the only B vitamin deficiency of which results in epilepsy in mammals including man.²⁰⁶ The E.E.G. is normal within minutes of giving intramuscular pyridoxine.⁴⁰¹

It has been shown that pyridoxine is required for serotonin formation and that its site of action is in the decarboxylation of 5-hydroxytryptophan.⁸³

Evidence has been provided for a specific biochemical defect which would account for the reduced heme synthesis and therefore anaemia in animals ingesting diets deficient in pyridoxine and pantothenic acid.⁴³⁷ A microcytic anaemia develops in dogs and pigs with pyridoxine deficiency. One case of anaemia with giant stab forms responding to pyridoxine in man has been described.³⁴⁹ Dacie *et al.*⁸⁶ have suggested that there may be a secondary deficiency of pyridoxine and folic acid in refractory normoblastic anaemia.

The daily adult requirement of vitamin B₆ is 0.2–0.3 mg.

Riboflavine

(This substance is probably present in every cell and occurs in combination with phosphoric acid to form a flavine nucleotide.) This is often linked with adenylic acid to form flavine adenine dinucleotide (F.A.D.).⁴⁷³ (It is thought to be an essential link in the chain of reversible oxidation-reduction reactions on which tissue respiration normally depends. It is possible that the clinical results of riboflavine deficiency are relatively trivial because of the little destruction of the vitamin in the body plus the additional source derived from biosynthesis by bacteria in the large intestine.)

(Riboflavine deficiency in animals results in a failure to grow and it was this that led to its first isolation. In rats the skin and particularly the eyes are affected. There is no specific sign of riboflavine deficiency in the human.)

Pantothenic Acid

This is a component of coenzyme A and is concerned in the process of acetylation. In particular (it catalyses the conversion of oxalacetic acid to citric acid which is the initial step in the Krebs cycle. No deficiency symptoms have been reported in man.) An attempt has been made to induce deficiency of this vitamin in human volunteers who were also given a pantothenic acid antagonist. They

developed clinical and biochemical abnormalities suggestive of adrenocortical insufficiency and peripheral neuropathy. But this state was not immediately relieved by pantothenic acid alone (4 g. per day), but was rapidly and completely relieved by a good mixed diet with multiple vitamins.

(Pantothenic acid has been used in the treatment of post-operative paralytic ileus, diabetic neuropathy, and psychosis, without any clear-cut benefit. Further investigation has failed to confirm that it is of use in the "burning feet" syndrome. It has also been used in the treatment of the ataxia due to streptomycin sulphate.²⁸⁹)

Bean *et al.*¹⁹⁰ have tried to produce pantothenic acid deficiency in man with diet and omega-methyl pantothenic acid (a metabolic antagonist) and were unable to confirm many of the previous symptoms and signs claimed to be due to deficiency of this vitamin.

Vitamin C

In nature vitamin C can either be in the reduced form, L-ascorbic acid, or the reversibly oxidized form dehydro-ascorbic acid. The latter exists in only small amounts. Vitamin C has not yet been shown to be involved in any coenzyme complex.¹⁷³

The most commonly used method for estimating ascorbic acid is a chemical one in which indophenol dye is decolorized in an acid medium within a specified time.^{26, 174} Another method involves the use of an osazone reaction,³³⁴ and there are also biological and microbiological techniques for analysing this vitamin.

Ascorbic acid is the most active reducing agent known to occur naturally in living tissues. It is a simple sugar. Mapson²⁶⁶ has recently reviewed the transformation of D-glucose into L-ascorbic acid. The essential steps are the conversion of D-glucose to D-glucuronic acid (or lactone), which is in turn converted to L-gulonic acid (or lactone) and thence to L-ascorbic acid. Work has continued on the preparation of enzyme systems capable of catalysing these changes.⁷³

The result of vitamin C deficiency is scurvy. The only species known to need vitamin C in their diets are men, monkeys and guinea pigs. This is because in these three species there is a deficiency of the liver enzyme system required for the conversion of L-gulonolactone to L-ascorbic acid.⁵⁹ In human beings, the features of classical scurvy have been known for a long time. Of interest, was the attempt to determine the minimal dose of vitamin C needed to prevent scurvy undertaken by the M.R.C.¹⁷ In the 10 subjects, receiving no supplement of vitamin C, the first signs appeared after

17 weeks, and were enlargement and keratosis of the hair follicles on the upper arm, back, thighs, calves and shins, all being associated with hæmorrhages. After 26 weeks swelling and hæmorrhage of the gums appeared. After 32 weeks half of them showed an exacerbation of acne. None developed anæmia. Seven subjects were given 10 mg. of vitamin C per day and in most of them no abnormalities appeared for at least 264 days, but some showed some signs after 160 days. The volunteers taking 70 mg. of vitamin C daily showed no deficiency. Volunteers with clear-cut signs of scurvy showed a rapid response to a daily dose of 10 mg. of vitamin C. From this experiment, it is also clear that if vitamin C is detectable in the blood plasma in normal amounts the diagnosis of scurvy is untenable. The absence of vitamin C in the plasma is not diagnostic of scurvy because this occurs long before clinical scurvy develops. A better index is the content of vitamin C in the white blood cells. This does not disappear until about four months of dietary depletion and the absence of it in the white blood cells makes the diagnosis of scurvy virtually certain. The urinary content of ascorbic acid is a valueless guide because small amounts of vitamin C or some other substance reducing 2-dinitro-phenol-indophenol continues to be excreted in the urine even in the presence of obvious scurvy. Harris¹⁷¹ introduced a loading test to assess the content of vitamin C in the human body. The accuracy of assessment by this means is limited by: (1) variations in intestinal absorption; (2) variations in the rate of tissue uptake; (3) variations in the catabolism and rate of excretion of temporary excesses in the blood. On the whole, the loading test has proved of limited value in the diagnosis of scurvy.

The results of the Sheffield experiment suggest that there is no evidence to support the view that more than 30 mg. of vitamin C are required daily.¹⁷

Mode of Action of Vitamin C. There appears to be a deficiency in collagen formation and in the functions of specialized cells, the osteoblasts, odontoblasts, and ameloblasts in scurvy. Wolbach⁴⁴⁹ studied cartilage in guinea pigs with scurvy and came to the conclusion that the essential lesion was failure of the production and maintenance of intercellular substances. The cells of the cartilage cease to form matrix and become irregular in shape. The role of ascorbic acid in the synthesis of hydroxyproline has been further studied by Gould,^{157, 158} who found that hydroxyproline formation in subcutaneously implanted polyvinyl sponges is analogous to its formation in granulation tissue. A direct specific effect of ascorbic acid was demonstrated *in vivo* by the rapid hydroxyproline synthesis

and thence the biosynthesis of collagen caused by the introduction of relatively small doses of sodium L-ascorbate into implanted sponges in scorbutic guinea pigs. Gould stresses that there may be alternative pathways for the formation of collagen since its formation in tissue culture was independent of ascorbic acid.⁴⁴⁸ The intercellular substance associated with fibroblasts in the repair of scurvy is of the nature of a mucopolysaccharide. It would seem that in scurvy there is a failure in intercellular material to form connective tissue, bone, cartilage and dentine.

It is also known that vitamin C plays an important part in cell physiology. King²³⁶ has demonstrated the lack of phosphatase, esterase and oxidase in scorbutic tissue, and the reduced capacity of the cells to metabolize the amino-acids, tyrosine and phenylalanine as well as the diminished activity of many specific oxidative and hydrolytic enzymes.

The first and, at present, only positive biochemical lesion that has been demonstrated in scurvy is an abnormality of tyrosine metabolism. Sealock and Silberstein³⁶¹ showed that the urine of scorbutic guinea pigs contained hydroxyphenyllactic acid and hydroxyphenylpyruvic acid products from the deamination of tyrosine which the animal was unable to oxidize. Patients with scurvy when given up to 20 g. of tyrosine failed to metabolize it completely and tyrosyl products appeared in the urine. Ascorbic acid is also concerned in the biochemical system which converts folic acid into folinic acid. It is not known how important its reducing action is in biology.

The relationship of vitamin C to adrenal function has given rise to considerable controversy. Harris¹⁷³ has recently reviewed this as well as other aspects of vitamin C metabolism. It would seem that it is premature to form any definite conclusion, but it seems likely that the association will prove of limited significance in human pathology. As the evidence now stands it seems most probable that ascorbic acid by its reducing properties inhibits the oxidative conversion of cholesterol to cortical hormones and thus acts as a break in their production.²⁷² Booker *et al.*¹²⁹ showed that an increase in the cholesterol in the blood of rats, guinea pigs, and man was evident after large doses of ascorbic acid. It is probable that liver cholesterol released under these conditions is related to adrenal hormone function.

Anæmia is a common finding in scurvy and it seems that vitamin C is essential for the normal maturation of the red cell. This difficult subject was reviewed by Bronte-Stewart in 1953.⁵⁷

Vitamin E

The diversity of the biological manifestations of vitamin E deficiency and the extent to which substances chemically unrelated to vitamin E substitute for the vitamin in various test systems have complicated the delineation of a single role for this vitamin.

It was shown by Bam that certain anti-oxidants when added to animal diets deficient in vitamin E would delay the onset of deficiency symptoms.^{299, 302} It is not certain whether these compounds substitute for vitamin E or whether they act by sparing or protecting the vitamin already present in the tissues. The latter viewpoint is generally considered more feasible. Draper *et al.*¹⁰⁶ studied the effectiveness of methylene blue and *n,n*-diphenyl-*p*-phenylenediamine (DPPD) in substituting for vitamin E in the prevention of foetal resorption in rats. They showed that when given to the female rat it was able to prevent vitamin E deficiency and that this protection completely disappeared in the third generation, suggesting that it might have acted by sparing residual vitamin E which eventually disappeared. It was decided to try to see if DPPD could cure vitamin-deficient rats which had resorbed foetuses one or more times and it seemed that it could in fact take over the role of vitamin E. Two compounds related to DPPD allowed litters of healthy rats to be born to vitamin E-depleted mothers, while the unsupplemented group delivered no litters.¹⁰⁷ It has also been shown that methylene blue has a slight effect in preventing reabsorption of foetuses.⁷⁰

The relationship between vitamin E and muscular dystrophy in man has not been established. In experimental animals muscular dystrophy can be produced by vitamin E-deficient diet. When it is then given by injection the muscular dystrophy is cured. This is also achieved by giving hydroquinone.²⁶² Low serum vitamin E levels, increased susceptibility to peroxide hæmolysis of the red cells. Creatinuria has recently been reported in fibrocystic disease of the pancreas and has been thought to be due to a long-standing defect in vitamin E absorption. The metabolic effects were abolished by giving vitamin E.²⁸ In a series of autopsies on children with cystic fibrosis of the pancreas an excess of ceroid pigment was found in the smooth muscle fibres of the intestinal tract. This is also found in experimental animals on a diet deficient in vitamin E.

Selenium can prevent exudative diathesis in chickens on a torula yeast diet as can vitamin E.³¹² It has also been shown that inorganic selenium salts were remarkably effective in protecting against

necrotic liver cell degeneration which is commonly found in experimental vitamin E deficiency. Sodium selenite was shown to be 500 times as active as vitamin E. The amounts needed are comparable to those of some essential metal required because of incorporation into metalloenzymes and suggest the possibility that selenium is part of an enzyme essential for some oxidation-reduction reaction in which vitamin E acts as an anti-oxidant. All the experiments on vitamin E deficiency must be re-evaluated in terms of the selenium content of the diet.

Vitamin K

Vitamin K is necessary, possibly as a coenzyme, for the synthesis of prothrombin by the liver. The pure substance is called vitamin K₁, but there are potent synthetic compounds. In vitamin K deficiency there is hypoprothrombinæmia with resultant hæmorrhage. Deficiency of vitamin K may result from defective absorption as in steatorrhœa or from impaired synthesis of prothrombin in liver disease. It is normally synthesized by intestinal bacteria and antibiotic therapy may interfere with this.

Congenital idiopathic hypoprothrombinæmia is a rare disorder and usually responds poorly to vitamin K administration. Some authorities have claimed that the value of routine prophylactic vitamin K has not been clearly established in the newborn. A recent report on coagulation¹ studies in 26 cases of hæmorrhagic disease of the newborn has shown that the majority are due to vitamin K deficiency and that the administration of vitamin K is dramatically successful. Presumably the rarity of this disease in the U.S.A. and Europe is due to the prophylactic use of vitamin K. Excessive dosage of vitamin K is associated with a higher incidence of icterus neonatorum and kernicterus. The coagulation deficiency induced by the coumarin group of drugs is readily reversed by giving vitamin K₁ by mouth.

TRACE AND OTHER INORGANIC ELEMENTS

Background literature on the scientific and applied aspects of trace elements has been brought up to date.^{90, 447} There have been several recent reviews.^{45, 95, 351} The 1950 edition of McLester and Darby's textbook says:

"The occurrence of deficiencies of trace elements in herbivora has fired the imagination of many as to the possibility of similar deficiencies occurring in man."

“Despite the considerable amount of loose and uncritical discussion of trace elements and their deficiency in man, particularly as related to the quantity of these elements present in soil, it may be fairly stated that, with the exception of iodine, no acceptable evidence has appeared for the occurrence of them in the soil.”

Although Barcroft's definition¹⁴ of the properties of “trace elements” can be accepted, the term is still ambiguous. The current list of medical literature lists under this heading Al, B, Co, F, Mn, Se and Zn. In addition Cd, Cr, Pb, Ni, Rb, Ag, Sn, Ti and V have been surveyed in healthy and pathological human tissues and magnesium and copper must be mentioned.

Veterinary and agricultural science is today very alive to the far-reaching effects of deficiency of trace elements in soils acting to produce deficient growth directly of plants and indirectly of herbivorous animals.³⁵²

Because man is an omnivorous animal he is less likely to suffer from trace element deficiency. Except in very underdeveloped communities, if animal flesh and products come from animals which are fit to eat, the animal is likely to have extracted what he needs of these elements for growth and development from one source or another and man is therefore spared the search on his own behalf. This thought should not be pressed too far because iodine at once springs to mind as an apparent exception. Fluorine deficiency in relation to dental caries is another apparent exception. These two trace-element deficiencies constitute an important starting point in the consideration of trace-element deficiency in man.

Iodine

There can be no doubt about the importance of an internal or metabolic effect of deficiency of iodine resulting from deficiency in food or water. This statement does not in any way invalidate the potential importance of goitrogenic substances in food or water acting as conditioning factors to precipitate deficiency on marginal intakes of iodine. The recent death of McCarrison²⁵⁸ recalls the earlier stages of this interesting story. Modern developments are reviewed in Ch. 21. It is interesting to see how widespread iodine deficiency is in Central and South America where it has been thoroughly looked for. The use of iodate as a prophylactic has now been established. The efficacy of iodine had, of course, already been accepted, but it suffered from the disadvantage of being

unsuitable for national programmes of iodization of table salt in underdeveloped regions. This difficulty has been entirely overcome by the substitution of iodate.

An interesting example of mineral nutrient interrelationships is provided by the claim that iodine deficiency can be conditioned by the presence in the same drinking water of large quantities of fluorine.³⁷⁸

The distribution of endemic goitre mainly through the mountain belts of the world is, of course, attributable to the fact that iodine is very soluble and easily leached out of the soil under conditions of heavy rainfall. This is of considerable ecological interest because there is considerable evidence that throughout the tropical rainbelt of the world soils which might be regarded as fertile from the incorporation of a great deal of humus are, in fact, impoverished by the leaching out of soluble trace elements, and even macro-elements, by heavy rainfall.

Copper

The world-wide importance of iron deficiency is referred to below. There is a great deal of experimental evidence that copper is also required for the synthesis of hæmoglobin in mammals. It was shown as early as 1928 that although copper is not a constituent of the hæmoglobin molecule, it is required, presumably as some form of catalyst, for the incorporation of iron into hæmoglobin so that copper-deficient rats develop anæmia even when iron is provided in adequate quantity. This anæmia is hypochromic, as in iron deficiency, and is rapidly corrected by the administration of copper. On copper-deficient pastures sheep develop ataxic "swayback", a demyelinating disease, and cattle suffer from "scours" (chronic diarrhoea), although anæmia is not a regular feature. Copper metabolism is reviewed in various recent books.^{175, 447}

In clinical practice it was shown as early as 1931 that occasional cases of hypochromic anæmia in infancy could not be corrected by iron unless copper also was provided. Although it has been fashionable for manufacturers of therapeutic iron to incorporate copper in their more elegant and expensive preparations, there has never been any convincing evidence of anæmia or any other clinical abnormality resulting from copper deficiency in man beyond the first year of life. Its occurrence in the first year of life could reasonably be attributed to the fact that milk is a very poor source of copper. As soon as mixed feeding is introduced the likelihood of copper deficiency becomes remote. Balance studies have shown a requirement of

approximately 2 mg. per day for adults. Even very poor diets contain more than this quantity. The amount of copper in an adult human body is estimated to be between 100 and 150 mg. Serum copper levels have been studied in the South African Bantu.³⁹⁹

Very recently a new syndrome has been described in infants in which deficiency of both iron and copper in the serum is associated with œdema and hypochromic anæmia. It is not yet clear whether this syndrome is an inborn error of metabolism or whether it is simply a more complicated manifestation of dietary copper deficiency^{348, 381}

There has been considerable interest recently in the possible relationship of copper deficiency to mental illness. Current reports suggest, however, that there is no ætiological relationship, the copper deficiency in most cases resulting from perversion of appetite.^{200, 277} In a paper in Afrikaans by B. J. Meyer²⁷⁶ another publication on this subject is foreshadowed under the name of B. J. Meyer in the same journal in press. Interest in this field was presumably stimulated by the relationship of hepatolenticular degeneration (Wilson's disease) to the specific copper-protein compound in the plasma, ceruloplasmin.²⁷⁷ This interesting subject will not be discussed here because the disease is an inherited metabolic abnormality and is not obviously related either to copper deficiency or to copper excess in the diet.¹⁸

Fluorine

Fluorine is a micro-element, excess of which is undoubtedly deleterious to man. In many parts of the world where fluorine exceeds 1.9 ppm in the drinking water there develops after many years a condition of fluorosis characterized by very dense bone and severe spondylitis and arthritis. The period of exposure to high fluorine intake has usually exceeded 15–25 years.³⁰⁶ New variants of the classical picture have recently been described.¹⁰⁴

On the other hand, it has been shown that fluorine in the drinking water at levels between 0.5 and 1.0 ppm is protective against caries. In various centres in the United States of America fluoridation of town water supplies to the level indicated has been followed by a very marked drop in the caries rate. There seems to be no dispute over this conclusion. Opposition to fluoridation of water supplies stems from a fear of remote systemic ill effects, the appeal to personal liberty and the observation that the same results can be obtained by topical application of fluorine to the teeth.^{110, 328} For the latter reason it appears likely that the protective effect of fluorine is exerted locally through its action on the bacteria of the

gingival pockets. This may be another example of the effects of micro-elements on bacterial growth in the digestive tract (Ch. 3). If there is in fact, as suggested in the discussion on iodine, an inter-relationship between fluorine and iodine, this effect is probably exercised within the lumen of the gastro-intestinal tract, another example of interference of one nutrient with another in competition for absorption.

Cobalt

Cobalt, which has proved to be a most interesting trace element in veterinary medicine, may well also exert its action through an effect on bacterial flora in the digestive tract (Ch. 22).

The occurrence in Australia and other parts of the world of large pasture areas deficient in cobalt with a resulting disease in sheep and other ruminants aroused very great interest. The matter became more interesting when cobalt was shown to be an essential element in the molecule of vitamin B₁₂ since the cobalt-deficient sheep were anæmic. It would appear at present that in the absence of cobalt the flora of the rumen of sheep are unable to synthesize vitamin B₁₂. In spite of all this interest no evidence is yet forthcoming of cobalt deficiency in man. In premature infants cobalt therapy has stimulated reticulocyte counts but without rise in hæmoglobin or erythrocytes.²⁵³ The significance of this observation is very problematic in relation to possible cobalt deficiency in these infants.

Holly¹⁹³ claims that in human pregnancy anæmia, iron and cobalt give better results than iron alone. The significance of his differences is, however, doubtful.

Although it has been stated that man is unlikely to suffer from many trace-element deficiencies as long as he is omnivorous, there is no doubt that the effects of dietary trace-element deficiencies should be looked for among vegetarian people and particularly among vegans. In Ch. 13 the subject of vitamin B₁₂ deficiency in vegans is discussed. It is possible that such people may also be deficient in cobalt which is part of the B₁₂ molecule.

Selenium

Considerable attention has been devoted to the fascinating story of selenium or its selenite salts and their relationship to what Schwarz called Factor 3 (the third missing factor in addition to cystine and vitamin E) in the causation of acute massive liver necrosis in rats.³⁵⁴ The same factor was later found to be responsible for an exudative diathesis in chicks³¹² and white muscle disease in

sheep.^{290, 291} At the time, this interesting experimental work appeared to have no relationship to man and there is still no evidence that man ever suffers from selenium deficiency.

On the other hand, a recent review of arsenic and selenium in relation to United States Law about food additives¹³⁷ brings out some interesting points in relation to possible selenium toxicity. Until 1957 selenium had received attention only because of its toxicity. In 1949 the statement was made by Trelease and Beath⁴⁰² that "as far as we know selenium is toxic but never beneficial to animals or man". The protective dose demonstrated by Schwarz and his colleagues is 1 per cent of the chronic toxic dose which had been placed at 300–400 micrograms per 100 g. of ration.

In a 1960 review by Frost¹³⁷ the history is given of the claim since 1820 that arsenic was carcinogenic and the recent discovery that the alleged toxicity of arsenic is really due to selenium. There is a serious suggestion that selenium toxicity can be counteracted by arsenicals. This is all the more confusing since selenium has at various times been studied as a cure for cancer. Early references on the toxicity of selenium can be obtained in Moxon and Rhian's review.²⁸⁸

Frost's 1960 review finishes with the interesting statement "the idea that nature alone provides the only proper food for man is both shortsighted and incorrect. Nature is not beneficent in creating soils in some areas of the world so high in selenium that plants growing there prove toxic to animals which consume them. By the same token, however, some soils produce forage too low in selenium to protect sheep from an apparent deficiency of this element. Natural occurrence in foods of nutrients which may also be reported carcinogenic poses problems".

Before leaving the subject of selenium another interesting reflection may be made. Schwarz³⁵⁴ in his long researches into Factor 3 missed for many years and only later discovered the role of selenium because he concluded from the fact that dry-ashing of Factor 3 concentrates destroyed their activity, that the active principle must be organic. We must always remember that some trace elements are very volatile; iodine is an outstanding example.

Other Trace Elements

In the 1958 review⁴⁵ short references are made to manganese, zinc and molybdenum, all of which have been detected in enzyme systems in mammalian tissues. Only in the case of zinc among these three has there been any interesting development in relation to the health of man. Two zinc-containing enzymes, alcohol dehydrogenase

and glutamic dehydrogenase can be crystallized from the liver. This led Vallee *et al.*⁴¹⁷ to postulate that a conditioned deficiency of zinc might be involved in the causation of post-alcoholic cirrhosis. Serum zinc levels have recently been studied in outwardly healthy adults of different racial groups.³⁶⁹

Trace Elements and Protein

Reverting to the role of trace elements in plant growth, evidence has been produced from our own group that beans grown experimentally on deficient media appear to have abnormal amino-acid patterns.³⁵² Such mineral deficiencies could, therefore, have an effect on health in areas where dietary protein is marginal and amino-acid deficiencies (kwashiorkor) occur.

Does Disease in Man arise from Micro-element Deficiency in the Diet?

The case for iodine deficiency can be regarded as definitely settled in the affirmative. Has any evidence developed since 1952 which would justify a revision of the statement quoted in the first paragraph of this section? In the foregoing discussion the case for fluorine deficiency in relation to dental caries is accepted and it is allowed that where human diets are mainly or wholly derived from vegetable sources, a case might be built up in the future for cobalt deficiency. In both cases the mechanism would appear to be mediated through effects on bacterial flora in the digestive tract. The case for an internal or metabolic effect of deficiency of trace elements other than iodine has still to be made. This is perhaps not surprising as long as mixed diets are consumed, since flesh would probably not reach a development attractive to man's taste if it were seriously deficient in any nutrient. Iodine deficiency is, however, an exception to this argument and there seems to be no reason why this one element should be the only exception. Certainly evidence of the effects of dietary trace-element deficiencies should be looked for among vegetarian peoples, and particularly among vegans. On the other hand, the possibility must not be overlooked, as has been foreshadowed in the above discussion, that internal deficiency might arise either from antagonism between trace elements and other inorganic constituents of the diet, or be conditioned by disorders of internal metabolism.

There is also a suggestion from a pilot experiment conducted in our laboratory that trace-element deficient soils may affect the pro-

tein composition of plants grown on them. Beans grown experimentally on trace-element deficient media appear to have abnormal amino-acid patterns.³⁵² Such trace mineral deficiencies may therefore have an effect on health in areas where dietary protein is marginal and amino-acid deficiencies (kwashiorkor) are known to occur. They may also explain the discrepant reports from various centres and on various samples concerning the first-limiting amino-acid of maize.

From the above discussion it can be concluded that speculation about trace element deficiency and its effects in man cannot be regarded as ridiculous. On the other hand, the evidence for such effects should be examined very critically, because it is certain that speculation will outrun facts, especially in the case of diseases of unknown ætiology. McFadzean and Webb²⁶¹ made an experiment to test whether anæmia in African children in the Gambia might be responsive to fortification of iron therapy with copper, manganese, zinc and cobalt. Their experiments were carefully carried out on groups of 50 children with adequate controls. Greater increases were observed in the hæmoglobin levels of two groups given trace elements than in the case of two groups not receiving the trace elements, but the differences were not statistically significant. Nevertheless, the authors state "it is suggested that trace-element deficiencies in man may be shown in the future to be of considerable importance".

In 1956 Comens reported that the "rheumatic state" resulting both in man and in animals from the administration of hydralazine could be reversed by the administration of small amounts of manganese. It was suggested as a reason that manganese was related to certain enzyme systems essential for the integrity of connective tissues.⁷⁸ On the basis of this report Bepler and Rogers²³ reported on a double blind study of the effects of administration by mouth of manganese to two groups of rheumatoid arthritis cases over a two-month period. The results were inconclusive.

In 1955 and 1957 de Villiers^{100, 101} wrote to the *South African Medical Journal* suggesting the possibility that the geographical distribution of pregnancy toxæmia in South Africa might be related to deficiency of trace elements. He did not give any evidence to support this conjecture, nor did he specify which trace elements were under suspicion. No literature references were given in support of the theory. As far as the written word is concerned, therefore, this hypothesis is conjectural.

Stamler³⁷⁶ has commented on the effects of trace minerals in animals on a high-fat high-cholesterol diet. Thus evidence was

obtained indicating that vitamins, cobalt and magnesium may inhibit hypercholesterolaemia and atherogenesis.

There will doubtless be unreasonable speculation about trace-element deficiency and its effects in man. On the other hand, possibilities in this direction cannot be ignored and every lead should be critically examined, taking the group of vegans as a test case.

Some other Inorganic Nutrients

Although the following elements cannot be regarded as trace elements, in terms of Barcroft's definition, they are briefly mentioned in this section to complete the context. Iron is discussed in Chs. 13, e and 32. It constitutes a transition between the macro- and the micro-elements because, although present in the body in considerable quantities, it is present in the diet in small quantities and the body has had to develop a mechanism for conserving it. Calcium is discussed in Ch. 25, and sodium and potassium and their important interrelationships in Chs. 2 and 20. An interesting historical article on bone growth and nutrition was recently reviewed by Neuman.²⁹⁶ Magnesium deficiency is discussed in two recent reviews³⁰⁴ one of which ends with the statement "it seems fair to conclude that onset of psychosis or semi-coma plus signs of tetany, especially in circumstances with starvation and fluid and electrolyte loss, should suggest the possibility of magnesium deficiency. In short, if the stage is set, onset of a delirium tremens-like syndrome justifies a chemical and metabolic search for magnesium deficiency as a prelude to specific replacement therapy". Hansen has mentioned the possible value of magnesium therapy in the management of the fluid and electrolyte disturbances of kwashiorkor. He has evidence from balance studies that magnesium deficiency is frequently present and severe.¹⁶⁷ A similar report has just appeared from Jamaica.²⁸² Since most of the macro- or micro-mineral elements required by man come directly or indirectly from the soil it is interesting to note that the average amounts of 10 mineral elements in fresh vegetables vary widely between vegetables from different geographical areas and even from shipment to shipment from the same farm.³⁰⁵

CHAPTER 10

FOOD ADDITIVES AND RESIDUES

In the early 1950s public health authorities and the international agencies began to be seriously concerned about possible long-term effects on man's health of food additives. The matter was discussed at the Third International Nutrition Congress in 1954. A Joint FAO/WHO Conference took place in September, 1955.²¹⁴ Food additives were defined as "non-nutritive substances which are added intentionally to food".

The Committee set as its task "to formulate general principles governing the use of food additives, with special reference to their legal authorization, based on appropriate consideration of their harmlessness, their standards of purity, their limits of tolerance, and the social, economic, psychological, and technological reasons for their use, and taking into account the work in this field by national and international bodies as well as the suggestions contained in various reports submitted to the Conference". It recommended that priority should be given in future study to the following subjects in the order indicated:

- (a) food colours;
- (b) preservatives: (i) anti-microbial agents, (ii) anti-oxidants;
- (c) emulsifiers.

Hueper's outline for a cancer research programme "which would yield the greatest amount of useful knowledge concerning the hazards of these compounds" was reviewed in 1957.³⁰³

English law on food legislation including food additives was reviewed in 1956.¹⁶³ The activities of the Federal Food and Drug Administration of the United States are reviewed in 1960.^{96, 357} In the latter review the dilemma of both the administration and food industry is clearly stated. Six chemicals have been proscribed as "unsafe" while 500 have been released as "safe" and another 155 have been proposed for the "safe" category. However, hundreds of chemicals at present in foods remain unclassified. Industry has been given a year in which to satisfy the laboratory-test requirements of the new law with regard to the unclassified chemicals.

There is a useful review of carcinogenic relationships between

arsenic and selenium in Nutrition Reviews¹³⁷ which refers to a 1960 report from the National Research Council of the United States on carcinogenic hazards of food additives in general.

Probably as important for future concern, and falling outside the definition of food additives, are residual chemicals used by agriculturalists and veterinarians. These include a great variety of pesticides applied to fruits, vegetables, cereals, etc., and animal growth stimulants such as oestrogens. These are referred to as residues, although there is possibility of ambiguity in their distinction from additives. Two recent discussions on this subject are recorded here.^{327, 338}

CHAPTER 11

RECOMMENDED ALLOWANCES

SINCE the recommendation of the League of Nations Health Committee²⁴⁷ it has become customary for countries to lay down recommended allowances of common foodstuffs and specific nutrients.^{92, 131, 293} German and French⁴⁰³ allowances are referred to in Chs. 26 and 31. These recommended allowances are supposed to be based on a plus-allowance or margin of, say, 33 $\frac{1}{3}$ –50 per cent over the minimum requirements. This margin is to cover unusual needs conditioned by unusual exertion or stresses such as inter-current illness. The subject of recommended allowances has become confused and controversial for the following reasons:

- (1) It is felt that the methods for determining some minimum requirements are not beyond suspicion and may have been set too high.
- (2) The plus allowance or margin has been made unnecessarily broad.
- (3) The net result is that recommended allowances have become councils of perfection which are capable of achievement only in a small group of privileged countries and are not likely to be generally achieved even under the best international reorganization until there has been some decline in the present rapid growth of world population (Ch. 16).
- (4) It has become apparent in the last decade that in respect of calories and certain nutrients, over-consumption by the individual may be as dangerous as under-consumption.
- (5) Common foodstuffs for which figures are given in recommended allowances are themselves variable combinations of more elementary nutrients, and a figure for quantity is therefore unrealistic unless quality is also specified. This disadvantage has been comprehensively discussed in relation to protein foodstuffs and in respect of fats. It is equally applicable to carbohydrates which have up to the present not been seriously discussed in this context.

The five points made above represent the author's personal view in a complicated and controversial field.⁴² The UNO agencies,

WHO and FAO have been active in this field during the last decade. In 1957, FAO produced its *Calorie Requirements*.¹²⁵ A start has been made by the same organization on the problem of protein requirements.¹²⁶ In *Calorie Requirements* a *Reference Man* is defined as 25 years of age, healthy and fit for active work. He weighs 65 kg., lives in a temperate zone at a mean annual temperature of 10° C. "He consumes an adequate well-balanced diet, and neither gains nor loses weight. On each working day he is employed 8 hours in an occupation which is not sedentary, but does not involve more than occasional periods of hard physical labour. When not at work, he is sedentary for about 4 hours daily and may walk for up to 1½ hours. He spends about 1½ hours on active recreations and household work." This Reference Man as defined requires on an average for the entire year, 3,200 calories daily. A *Reference Woman* is described in comparable terms and is estimated to require 2,300 calories daily, and she is given appropriate additional allowance for pregnancy and lactation. Modifications of the basic allowance are then discussed in terms of activity, body size, ageing, and climate. Appropriate requirements for children at various ages are given and the figures range from 120 cal./kg. at 1 month to 100 cal./kg. at 12 years. In a chapter on alcohol the recommendation is made that since calories provided by alcohol are available for metabolic purposes, they should be included in the tabulation of energy value, using the figure 7.1 cal./g. of alcohol. Incidentally some of the metabolic and medical considerations underlying the consumption of alcohol are discussed in Ch. 31. In *Calorie Requirements* appendix chapters are provided on (1) the activity component in calorie requirements; (2) body fat content and its significance; and (3) a simple formula for relating body weight and calorie requirements. The requirement of calories is finely balanced because deficiency, especially during growth, will raise the requirement for the more expensive protein-rich foods which tend to be diverted away from their primary function of tissue-building. Excess, on the other hand, is the most important cause of obesity. This subject is discussed in Ch. 14. At this point it should be remarked that the majority of people, especially when young and when engaged in active pursuits, can eat more calories than are required for energy expenditure on work and temperature regulation without laying down excess of subcutaneous fat.

The FAO protein requirements are discussed in Ch. 7. This report, however, contains a valuable review of the concepts underlying such terms as *nutritive value*, *biological value*, *replacement value*, *digestibility*, *nitrogen balance index*, *minimum*, *average*, and *optimum*

requirements and recommended allowances. The same concepts are critically discussed by Hegsted.¹⁸⁰

Some difficulties resulting from laying down over-generous recommended allowances are well illustrated in the cases of calcium and vitamin C. In two contributed chapters in this monograph (Chs. 25 and 24) the requirement of calcium is discussed in relation respectively to adults and infants. Both contributors come to the conclusion, with which the author is in agreement, that recommended allowances for calcium have been set too high. Apart from the practical difficulty of implementation in an underdeveloped and over-populated world there are even possible disadvantages in overloading the intestine with calcium and there may be disadvantages in the heavy load of calcium presented to the kidney for excretion. References are given in the chapters referred to.

Another disadvantage of over-generous recommended allowances of calcium arises from the fact that cow's milk is an excellent source of calcium in the diet. Dietitians in developed countries, and particularly in the U.S.A., have therefore pressed, in dietary propaganda, the consumption of cow's milk at all ages to an extent which is probably unnecessary if not unwise. It may be unwise because this high consumption of milk has made a considerable contribution to the rising percentage of calories derived from animal fat in the diet of privileged people. This in turn may have contributed to undesirably high levels of serum cholesterol. The significance of this for ischaemic heart disease has been discussed in Chs. 8 and 19. It must be remembered that the skeleton provides a very generous reserve of calcium which can be drawn upon in times of temporary shortage without any disadvantage.

In the case of vitamin C, the disadvantages of over-generous recommended allowances are less apparent except for the factor of wastage and the difficulties of application in underprivileged desert population groups and in far northern climates in the winter.³¹⁵ The recommended allowance for the U.S.A. for an adult is 75 mg. per day. British health authorities have set a comparable figure at 30 mg. per day.³¹⁵ Studies undertaken some years ago on Witwatersrand goldminers showed that very much lower levels of intake are compatible with freedom from scurvy even in labouring men.

The problem was discussed as long ago as 1943.⁵⁵ The following digest summarizes the position as stated in 1943:

Fox and Dangerfield had found no clinical evidence of incipient scurvy in the great majority of Bantu mine-workers

on intakes of ascorbic acid usually judged to be inadequate. On the other hand occasional cases of scurvy did appear in the group under examination indicating, presumably, that the remainder were on the borderline of deficiency and could be precipitated into recognizable deficiency by any unusual stress. At the same time Jokl and Suzman could find no evidence of deterioration in the physical efficiency of these same men over long periods of time. Commenting on this, Brock pointed out that at least in the case of vitamin C, the *physiologically indispensable minimum* had to be assessed in terms of at least two criteria (1) the amount required to prevent any clinically recognizable manifestations of scurvy from appearing; (2) the amount required to prevent deterioration in physical efficiency, working power or resistance to infection. Both criteria could yet again be sub-divided into (a) basal conditions of work and exposure; (b) average conditions of work and exposure; (c) conditions involving heavy work or unusual exposure to infections and other stresses.

The whole subject was re-examined in 1956.⁴²² In terms of modern concepts it would appear that the physiological minimum for vitamin C might be set anywhere between 10 and 30 mg. per day according to the varying criteria summarized by Brock in 1943. A great deal of additional information is now available for assessing the state of saturation of the body, e.g. capillary permeability under standard conditions of testing, plasma ascorbic acid levels and the level of ascorbic acid in the leucocyte-platelet layer of the blood. The basic difficulty remains unchanged, however, since the 1943 discussion. In terms of the ICNND Report discussed below, the range of nutrient intake described as *low* is probably as wide in the case of vitamin C as between *deficient* (10 mg. per day) to *acceptable* (30 mg. per day).

Ascorbic acid, being a freely water-soluble vitamin, is probably easily absorbed and easily excreted by the kidney. Somewhere between 2 and 4 g. can be stored in the body, and when these stores are filled any balance of absorption from the gastro-intestinal tract is probably promptly excreted by the kidney. This constitutes no further disadvantage than waste. There is evidence also that vitamin C encourages the absorption of iron from the gastro-intestinal tract and this constitutes an indirect advantage for reasonably high intakes.¹⁵⁶ Another indirect advantage is that the high consumption of fruit and fresh vegetables required to give a

high intake of vitamin C means also a high intake of minerals and cellulose.

A report from the Interdepartmental Committee on Nutrition for National Defence of the U.S.A. (ICNND) gives a "suggested guide to interpretation of nutrient intake data".⁴¹⁴ In this report figures are given under the headings *deficient*, *low*, *acceptable* and *high*, for five vitamins, calcium, iron and protein. In discussing the value of the "high" figures the report says "good" or "satisfactory" would be advocated by many to replace this term, but admits that the "precise health advantages which attend these 'high' levels are the subject of much difference of opinion and little conclusive evidence". The figures given under the heading "acceptable" are much more realistic, e.g. for male adults ascorbic acid 30–50 mg. per day and calcium 0.4–0.8 g. per day. Hegsted comments that the ICNND Report is "probably the most objective estimate of current knowledge which has been made by an official group. Difficulties in terminology, semantics, and philosophy are still apparent". He believes that its evaluation in practice should give better definition of the meaning of an "adequate" or "optimum" diet, which "must be a major concern of everyone with serious and valid interests in this field".

The Translation of Recommended Allowances into Individual or Institutional Diets. Provided reliable data are available on the composition of foods, a table of recommended allowances can readily be translated in terms of a customary diet for an individual or for a group. Ultimately it is desirable that every population group or geographical area should have its own food composition tables since there is little doubt that soil composition may be reflected in food composition within a certain range,³⁰⁵ and since selective breeding of cereal and other agricultural products may greatly alter food composition. For example, the protein content of different varieties of wheat grown in different parts of the world varies by as much as 100 per cent.⁴⁴⁴

References are given to some presently available tables of food composition.^{124, 257, 415}

The technique and cost of preparation and provision of diets according to customary usage requires an intimate knowledge of the psychology and traditions of a particular population group. Since most of the initiative for this has come from the Western privileged nations, there has often been a regrettable lack of imagination in translating recommended allowances into acceptable diets for under-developed peoples. On the other hand, that translation can be

achieved most successfully. An outstanding example of successful application under institutional conditions has been the diet and food preparation for labourers in heavy industry on the Witwatersrand gold mines of South Africa. It is doubtful whether, in a real sense, there is any better-fed group of people. The nutritive value of the diet has been achieved by the application of recommended allowances through the traditional diet of a rural people with judiciously selected supplementation derived entirely from natural products.

The cost of the diet has been low because of the simple tastes of the Bantu people who traditionally rely largely upon maize as their staple source of calories.

The basis of this feeding is described by Schulz.³⁵⁰ Economy has been achieved in certain mines by having the canteen open 24 hours of the day and setting no limit on the food served. Experience has shown that whereas with limited hours there was a tendency for the labourer to take more than he required and to waste what he did not consume, he now takes just what he wants.

CHAPTER 12

INFANT FEEDING

CONSIDERATION of the needs of infant nutrition in underdeveloped countries has led to a reappraisal of many long-standing views current in the developed countries. This subject is critically assessed by Holt in Ch. 24. His review throws refreshing originality into the field. It is particularly interesting in its challenge to those who believe that the faster a baby grows, the greater has been the success of the mother or the attending pædiatrician. His challenge to the adherents of over-generous recommended allowances, particularly with respect to protein and calcium, is reflected in the discussion in Ch. 11 on recommended allowances.

Platt has been interested for many years in digestion in infancy which he has considered both in relation to milk formulæ and to the largely vegetable formulæ on to which children are so often weaned in underdeveloped communities. His thought-provoking contribution is recommended for study.³²⁰

It will be seen that in Ch. 24 Holt says: "The bottle-fed infant in a privileged society grows quite as well and is quite as free from disease as his breast-fed brother. Perhaps at the age of a year he weighs a little more, and certainly his development is quite satisfactory." In Ch. 22, on the other hand, György refers to "the generally higher resistance of the breast-fed infant when compared with infants fed cow's milk". These two statements may be taken as representative of two schools of thought.

This long-standing controversy on the relative methods of breast and artificial feeding has been taken a step further by a model study conducted in a rural district in Sweden. This classic study is reviewed in Nutrition Reviews.²⁹⁷ It compared four groups of children weaned from the breast at periods varying from 2 weeks to more than 6½ months. Full details are given of the post-weaning diet and it is emphasized that the results and conclusions have meaning only for the specific cow's milk formula that was used and cannot be applied to other types of cow's milk feeding. The differences which were observed were naturally most significant between the first group, breast fed for 2 weeks or less and the fourth group, breast fed for 6½ months or more, but similar trends were seen through the second and third groups. Biochemical differences

between the groups such as serum calcium, serum phosphorus and alkaline phosphatase could reasonably be attributed to differences in calcium and phosphorus intake. On the crucial criterion of resistance to infection those weaned from the breast during the first two weeks of life had significantly more infections than had the exclusively breast-fed group (probability of 0.1 or less). The figures are for incidence of acute infections and no information is available about the severity or duration of the infections. It was not clear whether significantly higher gamma globulin levels in the first, second and third groups when compared with the fourth group were due to the higher incidence of infection or to the longer duration of cow's-milk feeding. This very fine and carefully controlled study therefore adds comparatively little to a solution of the controversy although it tips the balance in favour of reduced incidence of infection in fully breast-fed infants. It is unlikely that any more convincing evidence will be available for a long time so that the two schools of thought can continue to hold their points of view in a friendly spirit.

The physiology and practical applications of human lactation have been reviewed in a long series of articles by Hytten *et al.*²⁰⁸ under the title *Clinical and Chemical Studies in Human Lactation*.

In Ch. 24 Holt deals in some detail with the comparison between traditional artificial formulæ based on the composition of cow's milk and the more recent humanized formulæ which contain less protein and minerals, particularly calcium. He concludes: "The trend in recent years has been a return towards the breast milk formulation in artificial feeding. Future work may reverse or accentuate this trend. There have been many such reversals in the slow and painful path by which knowledge is gained." In this context his statement that "the need for a generous intake of calcium to make sound bones and teeth has been widely stressed by nutritionists, in spite of the fact that calcium deficiency is virtually unheard of in well-developed countries and that students of caries no longer attribute this disorder to a lack of calcium" is very relevant to the discussion in Ch. 25 on calcium requirements. In his McQuarrie lecture,¹⁹⁵ referring to the combined effect of calories and protein in artificial formulæ in advancing the rate of growth of children beyond that normally achieved by breast feeding, Holt asks the very relevant question: "I would like to be sure that in the nutrition field what we are getting is *better*, not just *bigger*." This matter is referred to also in sections headed, Diet and Stature (Ch. 14) and Recommended Allowances (Ch. 11).

A suitable and challenging comment on which to end this section is extracted from Platt.³²⁰ Commenting on the statement of the opening speaker at a panel discussion that "seen from several angles, infant nutrition is still an open chapter", Platt says, "presumably *open chapter* means little is known about the subject: we are in substantial agreement with him from the angle of digestion in infancy."

CHAPTER 13

THE EFFECT OF MALNUTRITION ON INDIVIDUAL SYSTEMS

MALNUTRITION may have general effects on the body which are discussed in Ch. 5. It may also demonstrate its effects in the first place through individual systems of the body. Some of these effects are now considered.

MALNUTRITION AND THE HEART

Certain aspects of the effects of malnutrition and undernutrition on the heart are classical although even some of these are at present in need of review. Little is known about the effects of acute starvation except that the heart tends to decrease in size with loss of body weight provided cardiocirculatory failure or fluid and electrolyte imbalance have not yet supervened. The effects of chronic undernutrition have been recorded by Keys *et al.*²³⁵ In considering the effects of deficiency of individual nutrients there is little doubt that deficiency of thiamine in the diet leads, after reserves of thiamine have been used up, to alteration in the electrocardiograph and functional efficiency of the heart. If the deficiency is severe or prolonged cardiocirculatory failure supervenes.⁴⁵² The classical picture of wet beriberi is, however, a late and complicated picture because in endemic areas there is usually also deficiency of protein (amino-acids) and often of other nutrients.

The broader subject of the oedema of malnutrition is dealt with in Ch. 20. The review in these chapters covers the respective contributions made to the oedema through many mechanisms, metabolic, renal and cardiocirculatory. It also covers both acute and chronic varieties of nutritional oedema. The effects of malnutrition on the myocardium, or cardiac organ as a whole, cannot be considered in isolation from all these other mechanisms which contribute to the total picture of oedema in states of malnutrition. In the following pages, however, special consideration will be given to the effect of malnutrition on the heart itself and particularly on the myocardium. They are best considered under the headings *acute* and *chronic*, although there is considerable overlap.

The subject can best be approached by considering the more acute

disturbances at a stage before they have produced oedema or congestive cardiac failure. The best defined of these is cardiac thiamine deficiency which can certainly occur without oedema or the classical picture of wet beriberi. Schrire and Gant have recently reviewed their experience in this group.³⁴⁷ They believe that there is a clinical and electrocardiographic picture which is characteristic, particularly in the sequence of events following administration of thiamine. There is a sequence of changes in the S.T. segment which gives the superficial impression that the electrocardiographic picture is becoming worse while the patient is obviously improving clinically (see pp. 30 and 31).

Many of the cases included in their series by Schrire and Gant were chronic alcoholics. It would be fallacious to believe that a chronic alcoholic is likely to be suffering from deficiency of thiamine alone and therefore the role of thiamine in the ætiology of their group of cases is established only inferentially from the effects of therapy with thiamine. It must be remembered, however, when considering response to treatment that these patients on admission to hospital had the additional benefits of recumbancy and a good all-round diet. In fact, it is doubtful whether in southern African cases of thiamine deficiency are ever encountered in the relatively pure form encountered in peoples of the Far East who use white rice as a staple source of calories. These reservations do not, however, question the important causative role of thiamine deficiency in disturbance of myocardial metabolism and therefore of cardiac function. It is important to realize, however, that deficiency of other nutrients such as oxygen and glucose and even electrolyte imbalance may produce, through a final common path, disturbances of myocardial metabolism which are not separable in their clinical and electrocardiographic effects. The same lack of specificity probably applies to the detailed description of T-wave changes in alcoholic cardiopathy.¹²²

In his review of kwashiorkor (Ch. 23) Hansen refers only in passing to myocardial disturbances in this condition. Smythe³⁷² has recently reviewed experience in this field and produced some very interesting evidence. In the first place the heart in kwashiorkor may be either small or enlarged; the factors determining this difference have not been clarified. On general principles one would expect the heart to be small in the stages of early and medium severity and to enlarge when the syndrome is severe and complicated by disturbance of fluid and electrolytes. The same factors might be presumed to underlie the differences in electrocardiographic pattern recorded by

Smythe.³⁷² His autopsy evidence confirmed the impression gained in life in that the weight of the empty heart varied from very low to high, e.g. the heart of one 16-month child weighed 23 g. (the new-born weight is 21 g.). In other cases the empty heart was definitely increased in weight and its microscopic appearance suggested that part of this increase might be due to oedema of the myocardium. There was no single histological feature or group of changes in the heart which could be regarded as characteristic of kwashiorkor. Comparing the changes found during life and at autopsy with the occurrence of unexplained death, Smythe concludes that "whereas there is no definite evidence of heart failure being the cause of death in kwashiorkor, enough evidence of disturbed cardiac function has been found to suspect that the heart may play some part in some fatal cases".

Smythe also comments on the similarity between visible changes in the myocardium and endocardium in some autopsied cases of kwashiorkor and similar changes in a group of adult cardiac cases sometimes referred to as "nutritional heart". In the opinion of the author, this term is apt to be misleading in the present state of our knowledge, at least in the context of adult pathology. The relationship of these adult cases to malnutrition is indirect and inferential and is open to the same objection as the term "nutritional cirrhosis of the liver" (see below).

MALNUTRITION AND THE LIVER

The anatomy of the liver and its physiology might lead one to expect this organ to be vulnerable to malnutrition. It is surprising therefore to find in Keys' "Human Starvation" that the liver is not listed in the index and is not directly discussed.

Experimental pathology gives abundant evidence of the direct and indirect effects of malnutrition on liver structure and function.¹⁴⁷ Pioneer work was summarized in Nutrition Reviews.³⁰⁰

The results of experimental pathology^{191, 270, 353, 354} can be summarized as follows:

- (1) Deficiency of the lipotropic complex (choline, etc.) leads to fatty infiltration of the parenchyma starting around the central vein and working outwards in the hepatic lobule.
- (2) Deficiency of protein leads to fatty infiltration starting at the periphery of the lobule and extending towards the central vein. These two forms of deficiency fatty change seem to be clearly distinguishable in experimental pathology.

- (3) Acute massive necrosis of the liver in mice and chicks results from a diet deficient in three factors, namely, cystine, vitamin E and Factor 3, recently identified by Schwarz as certain selenite salts or selenium. There is no preceding fatty infiltration, glycogen content remains unchanged and the cytology with ordinary stains remains virtually normal until shortly before necrosis occurs.

These three groups apparently result directly from malnutrition.

In addition there is evidence that the diet in experimental animals may affect the resistance and integrity of the liver when it is attacked by exogenous poisons, toxins and micro-organisms.¹⁶¹

The relationship between malnutritional fatty infiltration and necrosis on the one hand and cirrhosis of the liver on the other is complex. Early work was summarized in *Nutrition Reviews*.³⁰¹ Neither the sequential relation of fibrosis to the nutritional lesions nor its ætiology and pathogenesis are yet understood.⁴³³

The Human Liver. Surprisingly little is known for certain about the effects of malnutrition on the human liver. The subject was reviewed in 1959 by Leevy.²⁴⁸ The most definite evidence comes from controlled experimental work on kwashiorkor.⁴³³

Fatty Change in the Liver in Kwashiorkor. Fatty infiltration is an essential part of the pathology of the syndrome and the disappearance of fat from the liver has been followed by serial liver puncture during initiation and consolidation of cure. That initiation of cure has been achieved on mixtures of synthetic amino-acids, glucose and salts even without vitamins establishes the fundamental place of amino-acid deficiency in its therapy and therefore presumably in the ætiology of kwashiorkor and its fatty change. It might be expected, therefore, that the fatty change would have a perilobular start as in experimental amino-acid deficiency in animals. Histological evidence suggests that this supposition is correct, but unfortunately circumstances have not allowed actual confirmation by serial liver puncture during the forward development of the protein malnutrition which leads to kwashiorkor. The extent of the fatty change may sometimes be so severe as to make the liver architecture almost unrecognizable under the microscope. Nevertheless, it has been shown that on successful treatment there is complete restoration of normal liver architecture.³⁸²

Fatty infiltration of the liver occurs in humans under a great variety of other circumstances including diabetes mellitus, alcoholism, anæmia, tuberculosis, ulcerative colitis, infantile gastro-

enteritis, etc. It is uncertain to what extent and through what forms malnutrition may have a common bearing on all these causes of fatty change.

Alcohol and the Liver. The question of whether ethyl alcohol or any other constituent of alcoholic liquors may have a direct toxic action on the liver or whether the adverse effects are entirely due to secondary or conditioned malnutrition, has given rise to many interesting debates. In the 1930s Hurst²⁰⁷ claimed that a single alcoholic over-indulgence could disturb liver function tests in normal medical students. This work was not confirmed, and has been superseded by recent studies on serum glutamic oxaloacetic transaminase (S.G.O.T.) (see later).

On the other hand, since the demonstration by Strauss³⁷⁹ that alcoholics could be restored to health, including recovery of their polyneuritis, by a full and rich diet including vitamin B complex, while still consuming large quantities of alcoholic liquors, it has been believed that alcohol has little or no direct toxic action on the liver; its adverse effects are believed to be due to conditioned malnutrition. The trend of thought initiated by the work of Strauss has been repeated 23 years later from the same laboratory by Summerskill *et al.*³⁸⁴ who were unable to detect any adverse effect in response to 90–120 ml. of 95 per cent alcohol given daily to chronic alcoholics with liver disease. These writers went so far as to suggest that alcohol may have a place in the treatment of alcoholics with liver disease. More recently, however, experiments similar to those of Summerskill *et al.* have been repeated with more sensitive tests of disturbed liver function, namely S.G.O.T. and serum G.P.T.^{179, 264} These workers were able to demonstrate disturbed enzyme levels following the administration of alcohol to chronic alcoholics. This action of alcohol could be reproduced in chronic alcoholics who had been on a nutritious high-protein diet for five weeks, but it could not be reproduced in 12 healthy non-alcoholic individuals. Modern techniques, therefore, indicate that alcohol can upset liver function in chronic alcoholic subjects even after five weeks of nutritious dieting. Not all alcoholics behave in this way and normal individuals do not show the same effect. Since it appears that S.G.O.T. rises only when there is a liver cell necrosis,⁴⁶² the potential toxicity of alcohol to the malnourished or sensitized liver is considerable and should at least justify the orthodox advice to chronic alcoholics that they should abstain altogether from alcohol. The negative results of Madsen *et al.*²⁶⁴ on 12 healthy non-alcoholic individuals may probably be taken as denying the earlier conclusions of Hurst,²⁰⁷

but it is not clear that the last word has yet been said about the effect of alcoholic liquors on the functions of a normal liver. Klatskin,²⁴⁰ reporting to the Council on Food and Nutrition of the American Medical Association on the role of alcohol in the production of cirrhosis, concludes that whereas malnutrition accounts for many of the effects of alcohol on the liver, "other as yet unidentified mechanisms may be involved". French writers have frequently taken this view.

Although the matter must be left unsettled, the possibility must not be overlooked that the deleterious action of alcohol on the liver may be due in part to constituents of alcoholic liquors other than the ethyl alcohol. Such a possibility would be in line with common social experience that one liquor may produce more hangover than another and support the common social advice not to "mix one's drinks".

There is no doubt that chronic alcoholism leads to secondary malnutrition through the following mechanisms:

(1) Perversion of appetite. This leads to avoidance of foodstuffs containing vitamin B complex, especially thiamine. There is often also a deficient intake of protein. As alcohol is metabolized to some extent through the same channels as carbohydrate the net effect of the appetite perversion is to result in an abnormally low ratio of thiamine to effective carbohydrate intake upon which the thiamine requirement is dependent. In other words, a diet consisting of bread yielding 2,000 calories and alcohol yielding 1,000 calories will require at least as much thiamine as a diet containing 3,000 calories drawn from bread. The circumstances of the alcoholic subject's diet suggest also that he may be suffering from protein malnutrition, i.e. relative deficiency in quantity or quality (amino-acid pattern) of protein in proportion to a relatively generous intake of calories from starch. This view is confirmed by Scrimshaw *et al.*³³

(2) The well-known chronic gastritis of chronic alcoholism may be only the most obvious evidence of widespread disturbance of gastro-intestinal function which might impair the digestion or absorption of nutrients and disturb the pattern of bacterial flora (see Ch. 3).

(3) Frequent repetition of alcoholic over-indulgence undoubtedly leads to fatty infiltration and enlargement of the liver. This process is at first reversible in respect both of size and of histology when alcohol is withdrawn and a satisfactory diet consumed. In addition it can cause liver-cell necrosis, as evidenced by increase in serum G.O.T. levels.²⁶⁴ There seems no doubt, however, that under the

influence of long-continued alcoholism, abnormal fibrous tissue is laid down in the liver and eventually the pattern of late (Lænnec's) cirrhosis develops. The process has a superficial resemblance to the fatty change and fibrosis of the liver which can be studied in animals on pure nutritional deficiency and on combinations of nutritional deficiency with exogenous hepatotoxic agents. The process is best exemplified by experimental choline deficiency.

(4) The question may well be asked whether fatty change and subsequent cirrhosis in human chronic alcoholics is due entirely to the induced malnutrition or whether some part may be played by a direct toxic action of alcohol or associated aromatic substances in alcoholic liquors. This possible exogenous toxic theory is unpopular at present,³⁸⁴ but has not been finally disposed of.

(5) The pathological processes of fatty change and cirrhosis in chronic alcoholic subjects may undoubtedly be influenced by other external toxic agents such as viruses and drugs. There can be little doubt, however, that it can result purely from the consumption of alcoholic liquors and resultant induced or conditioned malnutrition.²⁴⁰

(6) No human counterpart has yet been described of dietary massive necrosis of the liver in mice and chicks, but obviously its relevance to acute liver necrosis and post-necrotic scarring in man must be considered. Although in man Laennec's cirrhosis and post-necrotic scarring are often clearly distinguishable at autopsy, there are many intermediate cases in which the distinction cannot be made. This is understandable if alcohol, dependent upon size of dose, is capable of producing both massive necrosis going on to post-necrotic scarring and fatty change going on to Laennec's cirrhosis. The complicating effect of exogenous agents such as viruses might then be expected to produce a great spectrum of final results in the architecture of the liver. Such a concept of multiple ætiology might explain the interesting differences between Laennec's cirrhosis as seen in the alcoholic in Boston and the cryptogenic variety seen in London.³⁸³

Influences, other than Alcohol, Contributing to Chronic Liver Disease in Man. By analogy from animal experiments one would suspect that in human liver necrosis, fatty change and cirrhosis may each, or in varying combinations, result from malnutrition acting alone or in combination with hepatotoxic agents. When this hypothesis is compared with clinical experience, it must be concluded that although the fatty change of kwashiorkor can result from malnutrition alone, there is no direct or final evidence that

necrosis or cirrhosis may result in man from malnutrition alone; there is very suggestive evidence, however, that they may result from the combination of malnutrition and hepatotoxic agents.³⁵

The extent to which the human liver can be protected from, or rendered sensitive to the effects of hepatotoxic agents by habitual dietary patterns or by therapeutic diets is a matter which has been in dispute. After intensive long-term and well-controlled experiments on the effect of therapeutic diets in virus hepatitis during the Korean war, the conclusion was reached that the optimal therapeutic diet for infectious hepatitis should contain 150 g. each of protein and fat.⁶⁷ Another commonly held view is that the patient may well be left to select whatever diet his taste dictates. Common sense and clinical sense combine to question rigid adherence to either view. It is admitted that the hepatitis virus is probably capable of causing necrosis of the liver and death even in people who have habitually consumed an optimal diet. This is evidence for the potential lethality of the virus rather than evidence against the protective effect of diet. Secondly, it will be freely admitted that the difference between a good and a bad outcome in an epidemic of virus hepatitis is determined by many factors other than the habitual diet. This seems evident by analogy from the account by Kirk²³⁸ of the epidemic of yellow fever in the Nuba Mountains. The effect of the virus varied in the community and even in a single household between the extremes of death from hepatic necrosis and the appearance in the serum of protective antibodies without recognizable illness. Such variability within a single household could hardly be attributed to varying individual consumption of a habitual household diet. At least if such variations had played any part it must be small compared with other unidentified variables. The role of exercise, for instance, has been much discussed.^{15, 67} The conservative recommendation in the 1955 report seems reasonable. The protective effect of diet is discussed also in the section on diet and general resistance to infection (see Chs. 14 and 29).

Another interesting speculation comes from epidemics of so-called "bread poisoning" arising from contamination of wheat with synecio, a known hepatotoxic agent.³⁶³ The circumstances of these epidemics suggest that the lethal and serious effects of synecio poisoning result only in persons subject to malnutrition and/or undernutrition. It is only in famine years that the very poor growth of the wheat plant enables the small synecio plant to be reaped and threshed with the ear of wheat. It is interesting to speculate whether the amount of synecio alkaloid consumed could cause acute and fatal

necrosis of the liver if the subjects were at the time well-nourished. There is no evidence on this score, but a detailed epidemiologic survey is long overdue. It seems clear that, as in the case of yellow fever in the Nuba Mountains, there was great variability within a single household in the effects of the "bread poisoning". It is interesting to comment here that the histopathology of synecio poisoning both in man and in the experimental animal shows a concentration of the lesion on the hepatic venules (a Chiari lesion). This observation is relevant to veno-occlusive disease (V.O.D.) of Jamaica and the West Indies which occurs in the same communities and at the same ages as kwashiorkor.³⁵ This observation links up with the following discussion on the ætiology of endemic Bantu cirrhosis and primary carcinoma of the liver. In this latter discussion it is postulated that long-continued protein malnutrition may condition the liver to an abnormal susceptibility to hepatotoxic and carcinogenic agents in the environment.

Endemic Cirrhosis and Primary Cancer of the Liver

The major contributions to knowledge in this field have come from the African continent and particularly from Johannesburg. The book "Perspectives in Human Malnutrition," by Gillman and Gillman,¹⁴³ and "Primary Carcinoma of the Liver," by Berman²⁴ were both published in Johannesburg in 1951 and can be taken as a starting point. Previous studies in Africa and elsewhere are reviewed in these books. The world distribution of high prevalence of primary carcinoma of the liver was mapped by Berman, and the ætiology and pathogenesis of the cirrhosis which almost always precedes it, were discussed by Gillman and Gillman. From these accounts it appeared that the high prevalence of primary carcinoma of the liver in certain areas of the world was a sequel to the cirrhosis. It also seemed clear that the cirrhosis was in many respects, if not entirely, different from that seen in most of the developed world and known generally as Laennec's cirrhosis. It is not suggested here that Laennec's cirrhosis is necessarily a morphologic or ætiological entity (see earlier discussion in this chapter), but the African variety appears to be in many ways distinct from the varieties seen in Europe and North America. The special ætiological factors which were suspected of playing a part in this African cirrhosis included tropical parasites such as schistosomiasis, viruses such as yellow fever, exogenous toxins such as synecio, prolonged dietary deficiency and siderosis (see below). More detailed study of the geographical pathology of these liver diseases coincided with interest in the

world epidemiology of kwashiorkor and with renewed interest in experimental nutritional diseases of the liver³⁹ it became apparent that some of the ætiological factors under suspicion were not universally operative and could therefore not be essential ætiological agents. It was already clear that the liver disorder was prevalent among the southern Bantu such as those from Basutoland and the Transkei who had never encountered schistosomiasis or any strictly tropical parasite. The term *tropical cirrhosis* was therefore unsuitable. At the New York Symposium³⁹ Brock, in reviewing the world distribution of kwashiorkor, which was already accepted as a result of protein malnutrition, pointed out that although the world maps of kwashiorkor and of high prevalence of primary carcinoma of the liver overlapped considerably, that overlap was not complete, especially in the Central Americas. It was not clear whether the gap in the occurrence of high prevalence of liver cirrhosis and primary carcinoma in the Central Americas, where kwashiorkor was endemic, was real or due to lack of reporting on adult liver disease. It was pointed out that, tempting as the term *nutritional cirrhosis* might be, it was a dangerous term in that it might convey the impression that ætiology had been established. Nevertheless, Brock reviewed in 1955⁴⁰ the very suggestive indirect evidence in support of a concept that prolonged protein malnutrition might render the liver susceptible to destructive agents which a well-nourished liver might be able to combat successfully.

In 1956 or 1957, largely through the enterprise of J. Gillman, an international conference was held in two sessions at Kampala, Uganda and at Leopoldville in the Belgian Congo, to discuss the problem of endemic primary carcinoma of the liver.^{386, 387} Contributions arising from further study of these problems since the Kampala and Leopoldville Conferences are at present being incorporated in a monograph.⁹⁴ Reviewing the evidence in 1959, Brock⁴⁶ summarized the Kampala Conference as producing facts and circumstantial evidence "suggesting that prolonged dietary inadequacy may play an important role in injuring the liver with subsequent appearance of primary carcinoma in some of the exposed individuals". Putting these thoughts in another way, we could postulate that long-continued malnutrition, especially of the type called protein malnutrition, could sensitize the liver to the action of cirrhotogens and carcinogens which would be successfully resisted by the liver of a well-nourished person. It must be emphasized that this is still only a hypothesis, albeit a reasonable one.

The difficult problem of the role of siderosis in the ætiology of

endemic cirrhosis and primary carcinoma of the liver is discussed below. Reviewing the subject in 1960, Higginson and Keeley¹⁸⁸ discussed the possible role of viruses, pellagra, general malnutrition, alcohol and siderosis. They conclude that "clear proof that the common liver lesions in the adult Bantu are due to dietary deficiency alone is not established by the evidence available from biopsy or autopsy material". It is doubtful whether anyone would seriously propose such a thesis. The alternative thesis here propounded is that chronic malnutrition plays an important contributory role in preparing the ground for the action of other ætiological agents in the production of what is essentially a disease of multiple ætiology. This is part of a general thesis relating the long-term effects of diet to the evolution of constitution (Ch. 14) in directions which promote a tendency in later life to degenerative disease, including cancer.

Siderosis

The problem of African siderosis complicates the already difficult problem of African cirrhosis and primary liver cancer. The co-existence of hepatic siderosis and cirrhosis might be due to a coincidence or the two might be related to each other in ætiology and pathogenesis. One fixed point in the discussion, however, is the fact that the widespread cirrhosis of the liver in the African continent, which is related to the high prevalence of primary cancer of the liver may occur with or without siderosis according to the area in which it is studied. (See Fig. 1 of Higginson's 1955 article.)¹⁸⁶

There has been ambiguity about the use of the terms siderosis, hæmosiderosis and hæmochromatosis.³⁹ This ambiguity is unnecessary if attention is given to the etymology of the words. In a recent symposium at the Royal Society of Medicine³⁹⁶ the terms are properly used. According to McLaughlin²⁶³ the term siderosis was coined by Zenker in 1866. It should be used to cover all forms of excessive iron in body tissues whether these be chemically or histochemically demonstrated. The other two words, from their derivation, should obviously refer respectively to siderosis and pigmentation arising from endogenous deposition from the blood. The use of the term hæmosiderosis could legitimately be extended to transfusional hæmosiderosis even though the blood from which the iron is derived is mainly exogenous. The term is obviously suitable for the siderosis resulting from hæmolytic and other mechanisms. Although, etymologically, hæmochromatosis implies abnormal amounts of pigment derived from blood, confusion has arisen because the greater part of the pigment in idiopathic hæmochromatosis is

iron-containing and the condition is associated with severe siderosis of organs. The exact ætiology and pathogenesis of idiopathic hæmochromatosis is still uncertain, but if it be accepted that this is a congenital defect of iron metabolism,³⁶⁵ presumably due to some enzyme deficiency, in which there is abnormal absorption of iron or failure of excretion of iron, then the term idiopathic siderosis would be more appropriate than idiopathic hæmochromatosis. It is unlikely, however, that current terminology will be altered. The same ambiguity of terminology complicates our approach to the prevalent siderosis of the African continent which has sometimes been called hæmochromatosis although it is unlikely that the iron pigment is derived from endogenous hæmoglobin.

The geographical occurrence of siderosis in southern Africa and elsewhere in the African continent was reviewed by Higginson.¹⁸⁶ Its morbid anatomical and histopathological features are compared with those of classical hæmochromatosis and it is concluded that there are several reasons for rejecting the theory of a common ætiology. The very controversial subject of ætiology is discussed and it is concluded that excessive oral iron intake is the factor of major importance. This review contains a full bibliography of publications up to 1955 on the subject. The views expressed have led to considerable controversy, triggered by an editorial in the *Lancet*,¹¹⁸ a letter by Higginson,¹⁸⁷ and a reply by Gillman *et al.*¹⁴⁵ A further report was made by Gillman.¹⁴⁴

The author has no intention of entering this controversy, nor of fully reviewing the literature. It is necessary, however, to point out its relevance to a discussion of the relationship of malnutrition both to cirrhosis of the liver and to siderosis. The nature of the problem can be stated as follows: It is established that in certain parts of Africa where siderosis is prevalent, dietary iron intakes may be as high as 100–150 mg. per day as a result of local customs of cooking and producing fermented gruels in iron pots. The iron excess in the body might, therefore, be a direct result of dietary iron overload; alternatively it might be due to or complicated by disturbance of the regulating mechanism for iron absorption and excretion. Such disturbance might be a direct manifestation of dietary malnutrition, or might be conditioned through a vicious circle mechanism. Deposition of iron in connective tissue might be simply a result of excessive quantities of iron in the body, but deposition of iron within the hepatic cell (cyt siderosis of Gillman and Gillman) might be due to abnormal metabolism resulting from complicated dietary deficiency, particularly malnutrition.

The excess iron, having gained entry to the body, is not readily excreted because an excretory mechanism hardly exists. Deposition in connective tissue seems to be a normal result of the presence of excess iron and such deposition appears to lead to fibrosis at least in the liver and pancreas. But iron is also deposited in the parenchymal cells of the liver (the cytosiderosis of Gillman and Gillman.¹⁴³ The Gillmans suggest that this may be due to abnormal metabolism of the hepatic cells, itself resulting from complex dietary deficiency. This possibility links up with the views of MacDonald and Mallory.²⁶⁰ They studied 211 cases of "hæmochromatosis and hæmosiderosis" in Boston, Mass., U.S.A. The only common link between these cases, many of which were alcoholics, and those of Gillman and Gillman would be complex effects of malnutrition. Siderosis was commonly present to a degree which makes MacDonald and Mallory question the validity of the traditional distinction from idiopathic hæmochromatosis. Support for this previously expressed unitarian concept has recently come from another group in Johannesburg, where Bothwell *et al.*³¹ conclude that "severe iron overload" in the Bantu is sometimes associated with the clinical and pathological manifestations typical of idiopathic hæmochromatosis". These views from Boston and Johannesburg do not constitute proof that classical idiopathic hæmochromatosis³⁶⁵ is not a genetic metabolic fault capable of causing severe siderosis even on an optimum diet. They do, however, stress the great complexity of the long-term metabolic results of chronic malnutrition.

A useful background review on the absorption and metabolism of iron appeared in 1959.⁴⁵⁷

Porphyria and Diabetes in the Bantu

The complexities of *endemic "nutritional" cirrhosis* in Africa and other parts of the underdeveloped world are further complicated by problems connected with porphyria and diabetes as exemplified in the Bantu of southern Africa. Eales,¹¹⁴ in reviewing porphyria, has expressed the view that the variety encountered in the South African Bantu is quite distinct from the Scandinavian and South African (White) genetic varieties¹¹³ and may be a result of chronic malnutrition and resultant disturbance of liver function. He says that the distribution of porphyria in Africa coincides with the distribution of hepatic siderosis. Keeley²³⁰ presented "six examples of a syndrome consisting of diabetes mellitus, porphyria cutanea tarda (P.C.T.) and siderosis, sometimes associated with cirrhosis of the liver." He concludes that the association is a significant one and

does not occur by chance. This observation links up with several recent communications on the prevalence of diabetes mellitus in the Bantu.^{61, 140, 322, 364} If there is a true increase it can hardly fail to link with dietary changes arising from urbanization.

ERYTHROPOIETIC SYSTEM

The relevance of problems of human malnutrition and under-nutrition to anæmia was the subject of a statement by the Joint FAO/WHO Expert Committee on Nutrition²¹⁸ in the following terms: "Anæmia constitutes a public health problem of great magnitude, particularly in the underdeveloped and tropical areas of the world. Malnutrition underlies most of the anæmias occurring in these areas where they affect particularly certain vulnerable groups in the population, i.e. expectant and lactating mothers, infants and young children. Since it is usually a chronic condition, anæmia impairs health and working capacity and hence leads to economic loss." The Committee also made the following statement about what, in this chapter, are referred to as hæmatinic nutrients. "Experimental studies in animals indicate that in addition to iron, vitamin B₁₂, folic acid and vitamin C nutrients such as pyridoxine, tocopherol and copper are intimately involved in hæmopoiesis, and that recovery from anæmia may be retarded by deficiency of protein or of a number of other essential nutrients. Iron, vitamin B₁₂, folic acid, vitamin C and protein are needed for blood formation in man, and it is probable that other nutrients found essential for recovery from anæmia in animal experiments are also required."

An invited chapter has therefore been included in this monograph (Ch. 32), and has been contributed by Woodruff who has been prominent in the study of the interrelations of nutrition and tropical disease in the ætiology of anæmia.

The classical advance in scientific hæmatology initiated in the 1930s led to clarification of the nature and role of dietary hæmatinics in the ætiology of deficiency dyshæmopoietic anæmias. Much of the subsequent work was confined to clinical studies in temperate areas where gross malnutrition was uncommon. The knowledge so obtained is now being extended and adapted to tropical conditions.

Iron Deficiency. It was early established that in a temperate environment dietary iron intake was always small in relation to iron turnover in the body and that iron deficiency was ordinarily prevented by the body's very efficient mechanism for conserving iron released by the break-up of hæmoglobin and for reutilizing it in erythropoiesis. Iron deficiency, therefore, is ordinarily precipitated

by abnormal losses of iron such as menorrhagia and chronic blood loss from the intestine. Because of the importance of menorrhagia as a cause of iron loss it became evident that iron deficiency and resultant hypochromic anæmia was far more prevalent in the female than in the male sex. In relation to pregnancy, the avoidance of 8-12 menstrual losses was more than offset by deviation of iron into the foetus *in utero* plus the deviation of iron into the newborn baby via lactation. Iron deficiency was therefore more prevalent in multiparous women. In men hæmorrhoids, peptic ulcer and gastric carcinoma accounted for the comparatively few cases of hypochromic anæmia. It was clear that among Western communities in temperate climates, diets consumed by economically underprivileged groups tended to be lower in iron content than among privileged groups. The greater prevalence of multiparity in the underprivileged groups accounted also for their much higher experience of definite and marginal hypochromic anæmia resulting from iron deficiency.

In tropical climates losses of iron may be greatly increased by parasites which cause loss of hæmoglobin into the fæces and urine. Ankylostomiasis has long been known¹³⁵ as a very important cause, and to a lesser extent schistosomiasis. More recently, it has been recognized that loss of iron through sweat and through desquamated epithelium may be an important cause of deficiency in tropical climates. It has been estimated, for example, by Foy and Kondi¹³³ that as much as 6.0 mg. may be lost by this route in a day. For the reasons given above it may well be that iron deficiency is the most widely prevalent nutrient deficiency in the world. The subject was exhaustively reviewed in 1959 by the study group on iron-deficiency anæmia of the World Health Organization.⁴⁴⁵ A briefer review appeared in 1959.⁴⁵⁷

In another section (Ch. 13) the problem of dietary iron overload is discussed in relation to nutritional siderosis. At this point it is interesting to note that in populations so affected the incidence of hypochromic anæmia is low.⁴²⁴ This belief has, however, been challenged.⁶³ The WHO Study Group estimated that: "About 2-10 per cent of the iron present in most European and North American diets is absorbed by normal people, while with iron-deficiency anæmia in these areas patients absorb from 20-70 per cent."⁴⁴⁵ The difficult subject of absorption of iron from the gastrointestinal tract was reviewed in 1958.²²⁴ It should be noted here that the mucosal block theory of Granick¹⁵⁹ is applicable only to small amounts of iron in the intestinal lumen and is easily overcome by

therapeutic doses of iron and probably even by the amount of iron contained in the Bantu dietary iron overload (50–150 mg. per day).

In what used to be known as idiopathic hypochromic anæmia it was suspected that achlorhydria and hypochlorhydria interfered with the assimilation of marginal quantities of iron in the diet and contributed to the development of anæmia. In this sense iron deficiency could be said to be conditioned by a gastro-intestinal defect, at least on diets containing marginal quantities of iron. Recent quantitative studies of iron metabolism, including studies with tracer techniques, have been reviewed.⁴⁵⁷ A recent review¹²⁰ discusses recent evidence on whether achlorhydria is a cause of iron deficiency or vice versa. The matter is left unsettled. This is probably another vicious circle mechanism.

Vitamin B₁₂ and Folic Acid Deficiency. The conditioning role of the gastro-intestinal tract in determining deficiency of a dietary hæmatinic (now known to be vitamin B₁₂ but at that time referred to as extrinsic factor) was beautifully illustrated in the classical experiments of Castle^{64, 65} and his group.

The subject was brought up to date by a valuable review of the megaloblastic anæmias and the role of vitamin B₁₂ and folic acid published in 1959.¹⁸⁴ Discussing the role of these vitamins in hæmopoiesis, Herbert says that “with the demonstration that in the mammal uridine may be incorporated into thymidine it was possible to conceive of cytoplasmic ribonucleic acid (R.N.A.) as the principal source of material for nuclear deoxyribonucleic acid (DNA)”. Failure in conversion of R.N.A. to D.N.A. would account for the increased R.N.A.–D.N.A. ratio of the megaloblast and this would form a basis for the understanding of megaloblastic hyperplasia. There is evidence that such a defect is not confined only to hæmapoietic cells since “megaloblastic” oral, gastric and vaginal epithelial cells have been demonstrated in patients with pernicious anæmia. Both vitamin B₁₂ and folic acid are essential in the synthesis of purines and pyrimidines and deficiency of either or both might interfere with the conversion of R.N.A. to D.N.A. This attractive theory is, however, not entirely supported in a review of the biochemical functioning of vitamin B₁₂ by Lester Smith.³⁷⁰ He quotes experiments of Connor Johnson and his colleagues which “failed to show any effect of vitamin B₁₂ upon the rate of synthesis of deoxyribonucleic or ribonucleic acid from any of several likely precursors in pigs or chicks”. Smith supports a more general protein synthesis hypothesis of vitamin B₁₂ activity. The precise metabolic relationship between vitamin B₁₂ and folic acid in respect of megaloblastic

hyperplasia has for long been somewhat mysterious, and is in fact not yet by any means understood.¹¹⁷ Herbert quotes evidence, however, to support a hypothesis that “vitamin B₁₂ influences folic acid metabolism, but there is no evidence at present that folic acid directly influences vitamin B₁₂ metabolism”. He goes on to state that “it is presently accepted that folic acid deficiency leads directly to megaloblastic anæmia; it is not yet certain that vitamin B₁₂ deficiency is a direct cause of the disease. The question is still open as to whether the megaloblastic anæmia which follows vitamin B₁₂ deprivation is a direct result solely of such deprivation or is partly the result of deranged folic acid metabolism caused by deficiency of vitamin B₁₂”.

Confusing and conflicting claims under this heading may be cleared up by a 1959 report from Marshall and Jandl.²⁶⁸

It appears that folic acid has often been used in experimental studies in doses which are far in excess of the physiological or replacement dose, and that in these doses folic acid may produce by “mass effect” reticulocyte response in a case which really requires vitamin B₁₂. When used in doses of the order of 250–500 micrograms daily a true folic acid response may be recognized and differentiated from the mass effect of say, 15 mg.

The whole subject of absorption and storage of vitamin B₁₂ and its conditioning by secretion of intrinsic factor is so thoroughly reviewed in Herbert’s monograph that it would be redundant to recapitulate here. Reviewing the causes of intrinsic factor deficiency, Herbert concludes that “Addisonian pernicious anæmia is itself probably not an etiologic entity, but rather a syndrome of several possible etiologies which will be detailed below”. He suggests at least three groups:

- (1) Hereditarily-determined failure of intrinsic factor secretion.
- (2) Hereditarily-determined degenerative gastric atrophy.
- (3) Gastric atrophy as the end stage of superficial inflammatory gastritis.

He reviews evidence that both iron and vitamin B₁₂ deficiency may cause reversible gastric atrophy so that even the hereditarily-determined cases of Addisonian anæmia may be precipitated in part by dietary deficiency. This suggestion links up with discussion in Ch. 14 on diet and constitution, in Ch. 3 with discussion of the vicious circle principle in the relation between diet and gastrointestinal function; also in Ch. 6 with a possible application of this principle to the role of folic acid deficiency in the production of steatorrhœa or intestinal malabsorption.

Straight dietary deficiency of vitamin B₁₂ (i.e. not conditioned by gastro-intestinal disorder) is thought to be rare. Because this vitamin is chiefly found in animal products dietary deficiency would be expected in vegetarians. The subject of dietary deficiency in vegans (i.e. strict vegetarians in distinction from ovo-lacto-vegetarians) was discussed at the Third International Nutrition Congress at Amsterdam in 1954.⁴⁴⁸ The subject is discussed in relation to the megaloblastic anæmias by Herbert,¹⁸⁴ who says "abstention from animal protein on religious grounds will produce vitamin B₁₂ deficiency if the abstention is complete". There may well be a vicious circle mechanism operating between folic acid deficiency, gastro-intestinal function and vitamin B₁₂ absorption.

The role of vitamin B₁₂ as a growth factor and the possible role of mild deficiency as a factor in the production of subnormal stature and health in underprivileged communities was reviewed by Howe²⁰¹ and is referred to in Ch. 14.

There can be little doubt, however, that dietary folic acid deficiency is quite common in underprivileged communities subsisting on mainly vegetarian diets. Assessment of its frequency is difficult because of uncertainty about metabolic relationships with vitamin B₁₂ and because of its possible role in determining mal-absorption in the intestinal tract (Ch. 6) and a resultant vicious circle (Ch. 3).

Protein-deficiency Anæmia. In their review of "Kwashiorkor in Africa"⁴⁹ Brock and Autret stated: "It is agreed by most writers that when parasitic infestation is absent or slight, anæmia is usually mild." A similar view was expressed by Trowell *et al.*⁴⁰⁵ They say "in uncomplicated cases of kwashiorkor it is not possible to detect any pallor of the mucous membranes. There is, nevertheless, usually a moderate degree of anæmia". The anæmia that is present is often due to deficiency of iron⁴⁰⁸ or folic acid.⁴²⁶ This comparative mildness of anæmia in what represents so severe a state of protein deficiency (see Ch. 23) seems surprising, and it has been postulated that the synthesis of red cell stroma and of hæmoglobin must be one of the highest priority calls on available supplies of amino-acids in the body. Robscheit-Robbins and Whipple in their experiments in dogs have shown "that the production of new red cell stroma and of Hb has a high priority in the total body demands upon reserve protein stores. In anæmia due to blood loss there is an increased stroma protein. Hypoproteinæmia causes no significant change in the stroma protein level"³³² The balance of evidence suggests the importance of protein deficiency in the production of anæmia,

especially in the context of zymotic disease.³²¹ Woodruff⁴⁵⁶ quotes Whipple⁴⁴¹: "One of the factors in the causation of the anæmia may be that hæmoglobin in its production can draw on plasma proteins and thus when these proteins are abnormal or deficient the production of hæmoglobin may be affected."

The natural history of anæmia associated with protein malnutrition was reviewed by Woodruff in 1955.⁴⁵⁶ The same author has brought the subject up to date in Ch. 32. He emphasizes the difficulty in assessing the role of deficiency of protein or amino-acids in the production of anæmia in man because the diets which characterize protein malnutrition, are deficient also in other important nutrients including the hæmatinic nutrients, vitamin B₁₂ and folic acid. The resulting multiple deficiency, perhaps complicated by liver dysfunction, presumably accounts for the morphological description of the anæmia of kwashiorkor by Trowell as "dimorphic anæmia".⁴⁰⁴ Woodruff's remarks on the role of albumin as a source for erythrocyte protein link up with a discussion in Ch. 7 of hypoalbuminæmia as a manifestation of protein deficiency and with a paper by Yoshimura⁴⁵⁹ on the effect of long-continued mild dietary protein deficiency on the erythrocytes and hæmoglobin.

Yoshimura,⁴⁵⁹ discussing adult protein requirements, emphasizes the sensitiveness of hæmoglobin and erythrocyte levels to marginal deficiency in protein intake. He claims particularly that when exercise is taken in the untrained state, hæmoglobin and erythrocyte levels may fall as a result of mobilization of their protein, used as a reserve, to allow for hypertrophy of skeletal muscle. The erythron then proceeds to compensate by increased activity, indicated by reticulocytosis. Provided dietary protein is adequate in quantity and quality this compensation may be complete with restoration of hæmoglobin and erythrocyte levels to normal. Either qualitative or quantitative deficiency of protein in the diet may interfere with this compensation so that a low-grade anæmia persists. It is possible that some of the fall recorded by Yoshimura on exercise is due to shifts in the fluid compartments of the body and his conclusions will doubtless be scrutinized critically. Their implications for protein requirements are discussed in Ch. 7. Foy and Kondi¹³⁵ would presumably also want to be satisfied that Yoshimura's subjects were not suffering from latent iron deficiency. Experimental studies are badly needed on the effect of pure amino-acid solutions on the hæmoglobin and erythrocyte levels in undoubted protein deficiency as exemplified by kwashiorkor. As far as the author is aware, no such studies have been completed.

In the meantime, in the face of conflicting data and opinions it would be reasonable to accept as a working conclusion that (1) although anæmia is always present in severe protein deficiency (kwashiorkor) its degree is often surprisingly mild, and (2) that when anæmia is severe it is due in part to deficiency of other hæmatinic nutrients such as folic acid. Studies such as those of Walt *et al.* indicate that folic acid deficiency is very prevalent in kwashiorkor.^{426, 427} On the other hand, it is possible, unless Yoshimura's results are discarded, that marginal levels of anæmia may be at least contributed to by suboptimal quantity or quality of protein foodstuffs (Ch. 7), especially under conditions of heavy work.

Anæmia in the Tropics. In the last decade, the special features of deficiency of dyshæmopoietic anæmias as they occur in tropical and underprivileged countries have been intensively investigated. There remain, however, many gaps in our knowledge still to be filled. The present position has been reviewed in Ch. 32 by Woodruff. At first there was great difficulty arising from the impossibility of dissociating the effects of tropical parasitism and the effects of malnutrition and undernutrition which are so prevalent in tropical climates. This matter is more fully discussed in Chs. 7 and 14. As it relates to anæmia Woodruff's review throws valuable light on many of the problems. Studies such as those of himself and his associates in the island of Mauritius have been valuable in that malaria has now been eradicated from an island community in which migration of population is minimal. There remains, however, the complicating factor of ankylostomiasis as a cause of abnormal iron loss. The work of Foy and Kondi in Macedonia, India, and more recently in Kenya has thrown light on several mechanisms, peculiar to the tropics, which may condition defective assimilation of hæmatinic nutrients from the gastro-intestinal tract especially when dietary intakes are marginal. It has also clarified the mechanism of excessive loss of iron through sweat and the shedding of epithelium under conditions of hard work in tropical climates.

Woodruff's review also brings out the mechanisms through which abnormal hæmolysis, as in chronic malaria, sickle-cell anæmia, etc., requires a greater rate of hæmopoiesis and so increases the body's requirements for vitamin B₁₂, folic acid and possibly other hæmatinic nutrients. The net effect, then, of underprivileged residence in the tropics is to expose the individual to marginal or inadequate intakes of hæmatinic nutrients. At the same time it increases his requirements for the same hæmatinic nutrients by promoting their

faster excretion (iron in sweat) or inducing a more rapid turnover (low-grade hæmolysis in malaria). These mechanisms differ therefore from those at the root of anæmia in temperate regions only in quantity and not in quality. Their net effect, however, on tropical community health is of enormous significance.

In the detailed discussion by Woodruff, there are links with several other chapters in this book. The effect of oral and particularly parenteral penicillin on megaloblastic anæmias as studied by Foy and Kondi links up with Ch. 22 by György on *Intestinal Symbiosis* since the mode of action even of parenteral penicillin may be exerted through its action on bacterial flora. This matter links up also with the discussion in Ch. 3 on the vicious circle mechanism between dietary deficiency and gastro-intestinal function.

The relationship of vitamin B₁₂ and folic acid also has great significance for tropical and underprivileged environments because of the very much greater prevalence both of pregnancy megaloblastic anæmia and of steatorrhœa and malabsorption (Ch. 6). In the nutritional megaloblastic anæmias studied by Tasker in Malaya³⁹⁷ results obtained by treatment with folic acid were not improved upon by prior or simultaneous use of vitamin B₁₂.

CHAPTER 14

LONG-TERM CUMULATIVE EFFECTS OF MALNUTRITION AND CUSTOMARY DIETARY PATTERNS

(a) Diet and Degenerative Diseases

IN an obituary note Robert McCarrison²⁵⁸ is quoted as saying that "Nature makes large scale experiments on man". Under great difficulties he studied the effect of different diets and methods of life on the health and nutrition of people in India, including a study of goitre. He tested his hypothesis by feeding rats on the whole diets concerned. He must obviously be regarded as a pioneer in the effects of diet on constitution.

It follows from an earlier discussion on constitution (Fig. 1, p. 25) that man's experience of morbidity and mortality may be determined by the long-continued action of favourable and unfavourable environment upon the genotype. If this be accepted, then careful thought should be given to the long-continued effect of environment in laying the foundations for many chronic diseases of uncertain and multiple ætiology and even of those degenerative diseases which have been regarded until recently as the inevitable penalty of ageing (e.g. arteriosclerosis). It is axiomatic that no one environmental factor such as malnutrition could be incriminated as the sole cause in any of these diseases. Its action could only be contributory in a constellation of multiple ætiology. Nevertheless, it may be an important cause since it may be the one which is most easily corrected with greatest resultant prevention of disease and promotion of health. This principle may well apply to the role of diet in the ætiology of many such diseases.

This concept has been developed particularly in relation to coronary heart disease (see Chs. 8 and 19). It is not suggested that the quality or quantity of fat in the diet, nor any other aspect of the dietary pattern, is the sole cause of the increase in prevalence of this disease in the last few decades in Western privileged nations. Rather it is postulated that the dietary pattern may be the most important of many causes since it is the one most easily corrected.

The same thought is obviously productive of a new approach when applied to such diseases as cancer. The role of diet in general

and of "protein malnutrition" in particular in the production of the high prevalence of primary carcinoma of the liver in many underprivileged nations throughout both the tropical and non-tropical world, has been thoroughly considered elsewhere (Ch. 13). In summary the view has been put forward that "protein malnutrition", continued over a period of many years, may render the liver more sensitive, or less resistant, to the action of cirrhotogens and carcinogens.

A similar contributory role on the part of chronic malnutrition or dietary imbalance has been discussed in relation to the ætiology of endemic cardiopathy of unknown ætiology (Chs. 13 and 30) and a number of other diseases.⁴⁰ Many of these diseases occur in tropical regions and have in the past been suspected of being due to tropical parasites or viruses. The study of geographical pathology has, however, made it clear that the geographical link with underdevelopment and malnutrition is far closer than with the distribution of tropical parasites. Protein malnutrition (Ch. 7), being the commonest and most important form of malnutrition in most of the underdeveloped world, has been specially studied, but the same principles apply to other forms of chronic malnutrition. In a symposium on *Protein Requirement and its Assessment in Man*, Levenson and Watkin²⁵⁰ discuss the effect of dietary protein on acute and chronic diseases. They discuss both acute and chronic infections and, among the chronic diseases, neoplastic disease and chronic liver disease. In view of the complexity of the problem they conclude that "it is not surprising that no firm final recommendations of the protein requirements of the sick and injured can now be made".

(b) Diet and Infection

There has been a puzzling contradiction of evidence on the relation of diet to infection. A recent paper by Dubos and Schaedler,¹⁰⁹ however, goes a long way towards a new basis for understanding. They have shown that "the diets most effective in assuring rapid growth of non-infected animals are not necessarily the ones that give the greatest resistance to infection. In other words, the ability to confer resistance is a criterion different from those usually considered by nutritionists". They point to the variability of different infections as "stresses" and therefore the variability of nutritional state optimal for each type of infection. Their views are illustrated by experiments involving different balances of amino-acids and of fatty acids in the diet. Clearly, we have much to learn before we can

define the diets most favourable to combating infections in man; but Dubos and Schaedler have at least shown that the effort is well worth while.

Relationships between nutrition and infection are the theme of Ch. 29, where the field is widely surveyed by Scrimshaw. The special aspects of infection of the gastro-intestinal tract and the balance of commensal micro-organisms of the colon are reviewed in their two-way bearing on nutrition in Chs. 3 and 22.

Some aspects of the relation between infection and protein requirements are reviewed in Ch. 28 by Platt, Miller and Payne.

(c) *Idiosyncrasy, Intolerance and Allergy to Food*

The ætiology of a wide group of serious and minor human disorders of uncertain and presumably multiple ætiology can be considered under these headings. Many of them have important psychosomatic relationships. At the allergy end of the spectrum they merge into serious and fatal diseases such as rheumatoid arthritis and the collagen or connective tissue diseases represented by polyarteritis nodosa and disseminated lupus erythematosus. At the psychosomatic end of the spectrum they merge into the psychoneuroses.

In an earlier section the opinion has been expressed (see above) that in all diseases of multiple and uncertain ætiology based in the constitution, it is necessary to consider the possibility that diet is contributing either directly or indirectly through its long-term effect on the evolution of constitution. Applying this concept to the problem under consideration, it is more than possible that both mechanisms are operative. Under the direct mechanism there can be no doubt at all about the important part played by immediate hypersensitivity reactions to certain foods. Acute allergic reactions through such mechanisms as urticaria and angioneurotic oedema, resulting from eating unusual foodstuffs such as shellfish and strawberries, are quite common, and are usually easily dealt with by dietary elimination. There is one interesting point for speculation; is the allergen concerned an intact protein? If so, why does it get through the barrier of the intestinal membrane? Alternatively, is it a polypeptide or some other protein residue? If so, does it have to be reconstituted into a protein allergen after it has passed through the intestinal membrane?

The permeability of the intestinal membrane to protein or other allergens will be discussed again in relation to chronic food allergies.

There is reason to think that chronic or recurrent food allergy is very common. In the absence of demonstrable blood reagins, scientific criteria for its diagnosis remain sketchy and difficult to apply. Strongly positive intradermal responses to injection of foods must represent an abnormal state, since they do not occur in the majority of people. But to conclude on this evidence alone that the patient's symptoms are due to food allergy is naïve. The difficulties of a critical approach to this subject are discussed by Kessler²³⁴ and Pratt.³²³

The terms *food intolerance* and *food idiosyncrasy* are often used in relation to conditions in which the specific criteria for establishing food allergy are absent. Of the two terms *food idiosyncrasy* is the easier to handle. There are many patients who get cardiac extra systoles after over-consumption of coffee or strong tea. Is this due to some constituent of the coffee or tea acting pharmacologically, e.g. caffeine, or is it possibly due to one of the aromatic constituents acting as a true allergen? Alternatively, is it a reflex result of motor or secretory abnormality in the upper gastro-intestinal tract from local irritative effects? Other patients suffer from disturbance of tone, movement and secretion in the colon when they eat certain foods. Idiosyncrasy of this type is common to citrus fruits and tomatoes. Again it can be asked whether the effect is exerted locally on the mucous membrane of the colon or whether components of the offending foodstuff are absorbed and act as endogenous allergens? We can at present only speculate on the answers to these questions and to related questions which arise in many fields of medical practice.

Food intolerance may well be a compound of either food allergy or food idiosyncrasy together with psychic and emotional factors affecting appetite, palatability and acceptability. It is even more difficult to study objectively. Food intolerance, even in the absence of demonstrable allergy, may be a good reason for eliminating certain items from a patient's diet; but it does not justify attempts at desensitization. In any case, the elimination should be temporary and not made permanent until long periods of observation have shown that the allergy or intolerance is permanent. Great care should be taken—especially in growing children and where there is intolerance to important foodstuffs such as milk—that the missing nutrients are substituted in readily available and palatable alternatives. This is seldom easy, and the personality of the child made “food conscious” may be harmed to a degree which is worse than the symptoms of the condition which is being treated. Food

intolerance, including food allergy, is often temporary and will yield to temporary elimination.

There is an impression that food intolerance and allergy are more common among civilized communities than among underdeveloped peoples. This impression has not been objectively verified. If it is true, it may be attributable to the obvious genetic link between allergy and psychosomatic disorders. Alternatively, it is necessary to consider the extent to which modern processing of food and the incorporation of food additives (see Ch. 10) may be responsible for the development of intolerance or allergy. On this score there is at present no satisfactory evidence.

Behind all this lies the stimulating question which can be posed in two opposite ways: (1) Why is allergy so common? In a textbook on allergy⁴¹⁸ a statement is made that "10 per cent of the population manifest frank allergy and upwards of an additional 50 per cent shows some minor allergic manifestations at one time or another". Is this because the allergic reaction is not qualitatively, but rather is quantitatively abnormal in that it is an exaggeration of a normal physiological response? At this point the question can be posed in the opposite direction; why do not all people become allergic? Can the answer to this question, whichever way it is posed, be sought in the basis of constitution and, if so, can it be related to the long-term effects of customary diets?

Food allergy appears to be particularly common in young children. Is this due to an exaggerated physiological response to artificial foodstuffs perhaps rendered harmful by modern processing and additives? We need to know the reasons why apparently healthy children develop intolerances or allergy to common foodstuffs which other healthy children eat with impunity? Certainly these reasons include the development of demonstrable reaginic allergy in only a small minority. What can best be called a "nervous temperament" is found in a high proportion, but may or may not be in part causative. An undoubted reason in some cases is deficiency of certain enzymes necessary for digestion, assimilation, or metabolism of specific nutrients: some of these have been carefully studied and identified as genetic deficiencies (e.g. phenylketonuria). The whole group has recently been surveyed³⁹⁰; they may be commoner than we have realized. If this is so, we may have to explain the higher prevalence in privileged people as due to absence of natural selection, and the association with "nervous temperaments" as due to genetic linkage. It will be surprising, however, if some acquired psychosomatic mechanisms are not uncovered and defined.

(d) Obesity

One very important long-term result of feeding in its relation to constitution is the variety of obesity which can be called *idiopathic* or *constitutional obesity*. This is usually distinguished from *endocrine obesity*, resulting from endocrine disturbances which are relatively well understood. This understanding is only partial and *constitutional obesity* may well have an endocrine basis which is not yet understood. If the term malnutrition be accepted in its widest sense as covering the results of consumption of an excess of calories with or without imbalance of foods and nutrients then *exogenous obesity* and *constitutional obesity* may be classed respectively as examples of dietary and conditioned malnutrition.

The term exogenous obesity should be used when the cause is obviously the consumption of a diet containing such a number of calories or such a balance of foods as would produce obesity in the great majority of subjects; familiar examples are the obesity of adolescents in a residential institution, the diet of which contains excessive starch calories and the obesity of chefs, cooks and obvious "guzzlers". Where there is any doubt that the obesity is either exogenous or due to known endocrine syndromes it should be called *constitutional obesity*.

The ætiology and pathogenesis of *constitutional obesity* has recently been discussed,^{90, 447} but the last word has not been said. Undoubtedly compulsive eating plays a part, but nobody has yet explained why some "fortunate" individuals can eat excessively and not become obese, while other "unfortunate" individuals become obese on diets which are really very moderate. The answer must lie in small differences between individuals which reflect themselves in differences of catabolism or anabolism or in the mechanisms which control deposition of fat in subcutaneous tissue. The latter mechanisms may be nervous or humoral and they are not at present understood.

There can be little doubt that the sophistication of privileged diets plays some part in the development of constitutional obesity. They do so in part by titillating the appetite and by encouraging consumption of "empty calories". The resultant changes may well initiate a vicious circle through the modification of constitution in such a way that it develops altered states of catabolism, anabolism or fat deposition. A recent article⁷⁶ discusses the role of the rate of ingestion of diet on regulation of intermediary metabolism or the difference between "meal eating" and "nibbling" on the metabolic and enzymatic machinery of the body.

The hazards of obesity are well known and thoroughly considered in many textbooks and reviews. Orthodox correction by restriction of calories in a diet containing all required nutrients, other than empty calories, in optimum quantity, and by restriction of appetite through educational, psychological and pharmacological means is reviewed in the textbooks by Davidson *et al.* and Wohl and Goodheart.^{90, 447}

Of many quack diets for the relief and prevention of obesity the latest is that capitalized in a recent popular book "Eat fat and grow thin". The origin of this specious theory in some short-term metabolic experiments by Kekwick and Pawan²³² was reviewed in a *Lancet* editorial.¹¹⁹ Kekwick and Pawan have disclaimed responsibility²³³ for the ideas underlying this popular high fat regime for the reduction of obesity. Olesen and Quaade³⁰⁸ have put the theory to critical test with negative long-term results. They attribute the short-term results to shifts in body water, an explanation not fully accepted by Kekwick and Pawan.²³³ It is likely that this type of dietary modification can be written off as an effective contribution to the difficult problem of the dietetic control of obesity.

It is customary to allow a range of normal of from -10 to $+10$ per cent of standard mean for age and height when attempting to define the normal weight of an individual. This range of normal about the mean is obviously necessary for statistical purposes, but it makes the actual determination of normal weight for an individual very difficult. A certain amount of judgment and discretion has to be exercised after going carefully into the body build of the patient's antecedents and family. New tables of weight standards for men and women have recently been published by the Metropolitan Life Insurance Company of New York.⁹

(e) Diet and Stature

In general, privileged populations are taller and heavier than underprivileged populations. There is some evidence that among developed nations there has been an increase in mean stature and weight over the last few succeeding generations. Within a given developed nation children from economically favoured areas are taller and heavier than children from economically underprivileged areas.³⁰⁵

On the other hand, there can be no doubt that both weight and stature are genotypically determined into a preferred channel of growth which may be retarded temporarily or permanently by



FIG. 8. The effect of malnutrition on size and stature. The children are of identical age and no history of serious illness was given. Allowance must of course be made for genetic difference.

unfavourable environment, including undernutrition and malnutrition, operating through complex pathways of metabolism and endocrine balance. This principle is utilized in the study of child growth according to indices such as that of Wetzel.^{269, 380, 440}

Among the environmental influences on growth the endocrine glands are of even greater importance than nutrition. They seem to be the main influence through which the genotype determines weight and height and they may operate to increase these indices even in the face of quite considerable undernutrition and malnutrition. Nevertheless, diet may affect stature and weight, not only directly but also indirectly through its effects on the endocrine glands (see Ch. 27). Nevertheless, it is becoming increasingly apparent in experimental work in animals that feeding in infancy may, to some extent, determine permanently the size of the animal. A critical long-term experiment in this field carried out in the laboratory of R. A. McCance at Cambridge has several times been quoted although it has not yet been published.^{162, 442} One aim of this experiment was to determine whether the effect on growth of variations in the quantity of maternal milk obtained during breast feeding would be temporary or permanent. Rats of identical genetic strain were used. Several new-born litters were mixed up and divided among the lactating dams in such a way as to give only a few to some and larger numbers to others. The young rats were subsequently weaned on to a regular commercial ration fed *ad libitum*. At the end of the growth period the rats which had been suckled in small litters remained larger than those which had been suckled in large litters. The implications of this experiment in relation to the stature of man are interesting and important. György¹⁶² has applied them to conjecture about the effects of early nutrition in determining the small stature of the Japanese people. The same conjecture could, of course, be applied to other nations of small stature. It has also, of course, disturbing implications for the principle of assessing child nutrition through the principle of the growth grid. This principle is based on the assumption that there is a genetically determined preferential or optimum channel of growth for each individual. It also has interesting evolutionary implications and Holt's comment might well be requoted (see Ch. 24) in the context of the increasing stature of Western nations. He would like "to be sure that in the nutrition field what we are getting is *better*, and not just *bigger*". The example of the dinosaur should be kept in mind. He evolved to such a large size that he eventually became extinct.

(f) Diet and Longevity

On the whole, the privileged have greater life expectation than the underprivileged. This is doubtless due to greater application of the favourable influences shown in Fig. 1 (p. 25) to be operating continuously on constitution; these, of course, include good feeding. Is there any possibility that man may suffer from a surfeit of the favourable environmental influences, including good food? There is indeed much evidence, although some of it is indirect. The simplest example is exogenous obesity which undoubtedly reduces life expectation. The evidence reviewed in Chs. 8 and 19 suggests that excess or imbalance of dietary fat may encourage the onset of degenerative diseases such as ischæmic heart disease and perhaps atherosclerosis and its effects in general. In Fig. 1 the deviation of the lines representing healthy and unhealthy constitutions begins before birth and results in differences of duration of life. How far have these concepts been experimentally tested? In man this has so far not been possible; a beginning has been made with rats. Attention was drawn in 1959⁴⁶ to unpublished experiments by Widdowson and McCance at Cambridge on the effects of early feeding on ultimate size and longevity in rats. McCance²⁵⁵ has recently reported on some aspects of his work under the heading the *maintenance of stability in the newly born*.

In 1959 Ross,³³⁹ at a symposium on *Protein Requirement and its Assessment in Man*, reported on long-term studies initiated on rats in his laboratory eight years previously. These studies were directed towards an understanding of enzyme changes resulting from modification of diet. Over 1,000 weanling rats were studied during their entire life span. His conclusion was that "the lifetime feeding of different levels of protein, of calories, and of carbohydrate in otherwise adequate diets has been shown to be an influencing determinant or a modifying factor in the incidence of degenerative disease and in the length of life".

He reviewed previous literature in this field and his results are expressively shown in a series of figures. This article should be consulted for detail. It lays the best foundations yet published for an understanding of this difficult and important subject. He rightly expresses the opinion that "of more importance than the conclusions which have been obtained from these studies are the questions one is now able to ask". He then proceeds to ask a series of questions which are highly relevant to this discussion of trends in man. These questions are all inherent in an understanding of Fig. 1 and its implications for stature, longevity, constitution and resistance to stress.

CHAPTER 15

THE PREVENTION AND CORRECTION OF ACUTE DEFICIENCY

Fluid, Electrolytes, Plasma and Blood

IN Ch. 2 water and electrolytes are discussed as nutrients and the conditions which lead to acute deficiency are considered in principle. Ch. 20 impinges on the subject, but is written primarily from the point of view of the results of chronic malnutrition. There have been great advances in the last decade in the prevention and correction of acute deficiency of fluid and electrolytes. This may result from many conditions leading to impaired intake, vomiting with or without intestinal obstruction, and diarrhoea. Excessive sweating may contribute, particularly during febrile diseases and in tropical climates. Loss of blood or plasma may also contribute with the additional effect of producing deficiency of proteins, erythrocytes and hæmoglobin.

These acute disturbances can be prevented or corrected by the proper use of parenteral solutions, plasma or blood. Where intestinal obstruction is a complication continuous gastric aspiration will relieve vomiting and allow an estimate to be made of necessary parenteral replacements. Appropriate estimates must be made of loss of fluid through the lungs and both insensible and sensible perspiration.

Attempts to correct losses of fluid and electrolytes by guesswork have in the past led to inadequate or inappropriate fluid and electrolyte therapy and consequent overloading of the circulation. Gross errors of this sort should no longer be made in modern hospital departments, but there is still a tendency to overload the circulation with blood because of a naïve belief in the magical boosting power of blood transfusion. It is often necessary to remind surgeons that the circulating mass of hæmoglobin has, like any organ, a very considerable reserve when the individual is at physical rest, and that unnecessary transfusions of blood involve unjustifiable risks of pyrogenic reactions and sensitization to later transfusions when they become necessary. Without questioning the undoubted value of transfusions of blood or plasma, on appropriate indications, for the relief of hæmorrhage and shock, it should be pointed out that the erythron and liver have ordinarily very great power to manufacture hæmoglobin and albumin.

Parenteral Feeding. The daily needs of vitamins and minerals can usually be supplied by intravenous infusions, which, however, should only be used when oral feeding is impracticable or in the face of excessive losses or suspected malabsorption. The dangers of salt and fluid overload, particularly in the unconscious patient are to be borne in mind, while the ill-considered use of potassium intravenously is fraught with danger. Fat-soluble vitamins can readily be administered intramuscularly. Iron can safely be administered either intravenously or intramuscularly when, occasionally, oral iron is poorly tolerated or absorbed.

Where the administration and assimilation of protein is clearly impossible or inconvenient by the enteral route, sufficient protein for the needs of tissue repair and maintenance can easily be administered intravenously in the form of protein hydrolysate, amino-acid mixtures and plasma. The intravenous administration of 1 litre of plasma per 24 hours will provide between 60 and 70 g. of protein of high biological value. The latter is, of course, an expensive method of feeding, and one which is very seldom required.

Where parenteral feeding has to be relied upon completely it is essential to provide adequate calories, in order to conserve the body's protein reserves and avoid the wasteful use of parenterally administered protein as a source of calories. It is difficult or impossible to achieve this with intravenous carbohydrate; for example, 5 per cent glucose solution will have to be administered in 8 litres of fluid in order to yield 1,600 calories. Stronger solutions of glucose have certain disadvantages such as the hyperosmolarity which they temporarily produce, and because of a tendency to venous thrombosis. The relative advantages of fructose and invert sugar and of intravenous alcohol are discussed by Geyer.* No combination of these is easily made an adequate source of calories for parenteral administration. Intravenously administered fat, therefore, has considerable theoretical advantages. Its use has been thoroughly discussed by Geyer. There are still some technological problems to be solved and the exact nature and cause of pyrogenic reactions and "colloid reaction" are still to be determined. It is probable, however, that these will be overcome.

Concentrated Oral Feeding. Preparations are now available which provide in approximately 1 lb. of dried powder everything that the body requires during 24 hours to fulfil its requirement of protein, calories and all other nutrients. The protein source is usually skim

* References (a) to (f) given below are additional to those given in Ch. 17 (general references).

milk powder. The retail price is less than that of a single restaurant meal. Such preparations will not be applicable for a few days after certain gastro-intestinal operations but otherwise, except where there is severe disturbance of gastro-intestinal function, they are easily digested and assimilated. Their only disadvantage is a monotonous texture and taste. Parenteral feeding is therefore seldom necessary.

Vitamin Therapy. The need for the administration of vitamins through any medium other than a soundly balanced diet is in effect covered by the foregoing sections. Where there is known to be a serious deficit in the body of one or more vitamins, that deficit can be made up in a few days by oral feeding unless gastro-intestinal function is seriously impaired. In the latter case the vitamin or vitamins may be administered parenterally in quantity sufficient to make up the deficit. These quantities should always have reasonable relationship to the estimated daily requirement (see Ch. 11). The special position of hæmatinics is discussed in Chs. 12 and 32. Vitamins occasionally exert, and are legitimately used to exert, a pharmacological effect (for example, nicotinic acid) but this should be recognized as distinct from their nutrient effect.

The above remarks are in very general terms. For detail, the reader is referred to a number of recent comprehensive reviews. Clinical application has been thoroughly dealt with under the section *Special Feeding Methods*, in the textbook by Davidson, Meiklejohn and Passmore.⁹⁰ The whole subject of parenteral nutrition has been exhaustively surveyed by Geyer who quotes 659 references.

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CHAPTER 16

SOME GENERAL TRENDS AND THE FUTURE

World Population, Growth and Food Supplies

FIGURES given at an International Conference in Rome in 1954 were reconsidered and rediscussed at a symposium on "Humanity and Subsistence" in Vevey, Switzerland, in 1960.³⁹¹ The discovery during the Second World War of antibiotics and new chemotherapeutic and chemoprophylactic weapons and their internationalization during the 1940s and 1950s through the specialized agencies of the United Nations (FAO, WHO and UNICEF) has made possible a remarkable fall in mortality at all ages and parallel increase in life expectation. The term "death control" has recently been introduced to cover this remarkable phenomenon. In the Vevey symposium one speaker said "We have now reached a point where, if any one dies of anything other than senility, we feel that there is something radically wrong with our social organization". Under the prevailing medical and general ethic "death control" is unhesitatingly accepted as good and has been rapidly applied.

If it be accepted that the survival of three children from each marriage or customary union throughout the world would lead to a slow but steady increase in world population, then it is obvious that under the influence of "death control" families of four or more surviving children will lead to a rapidly expanding world population. This is the stage that has been reached in 1960.

"Death control" has come to stay, and if world population is not to expand rapidly there must be restriction of population increase. Although the term "death control" is unhesitatingly accepted as good, the term "birth control", which was introduced long ago, still has a mixed reception. The ethics of this problem, which are not relevant in this book, can be simply avoided by substituting the term "family planning". This term in the 1960s should be universally accepted as rational, good and ethical in the light of what has been said about "death control". It includes methods for enabling childless couples to have the children they desire. It includes also the methods whereby couples may avoid unplanned and undesired children (family restriction). The methods whereby family restric-

tion is achieved need not concern us here. The objective can be achieved by various methods of which at least one ought to be acceptable to people of every ethic. What does concern us here is the necessity for family restriction in the light of what has been said about "death control" and in the light of figures for recent population growth.

In broad terms the problem can be expressed as follows: An estimated world population of 2·8 billion will increase by the year 2000 to approximately 5 billion, and by the year 2050 to approximately 10 billion if the population trends of the last decade be extrapolated forward. Opinions may differ on whether these trends are desirable or undesirable; but there can be no question about the importance of the problem of whether food production can be increased to meet these rapidly increasing population figures.

According to the director of the Nutrition Division of FAO the yield of food from the present cultivated part of the world's land surface could be increased by from 50–100 per cent by better methods of agriculture, fertilization and pest control. It is estimated that the present arable area of the earth's land surface could be increased by perhaps 100 per cent. A great variety of technological methods have been devised for producing food from the oceans, and from lakes, rivers and ponds (culture of fish and algæ); increase of land yields by improved methods of agriculture, fertilization, pest control, harvesting, preservation and distribution are at present in the stage of development. Their potentialities for the future in improved food supply are difficult to estimate, but any one who says that anything is impossible is likely to find himself embarrassed within a decade. We must conclude, therefore, that an increase in both quantity and quality of foodstuffs proportionate to present rates of world population increase are not technologically impossible. They will, however, require great feats of human achievement in goodwill and organization. Has mankind the capacity and the will to adapt itself to these vastly changing circumstances?

Population increase in the underdeveloped world runs between 2 and 3 per cent per annum. It is estimated that in China the increase in food production achieved under a new planned economy may reach 8 per cent per annum. Can this sort of increase be achieved by methods other than those comparable with the colonies of bees and ants? In other words, can they be achieved by methods which preserve the accepted "Freedoms of Man"? The alternatives are staggering in their implications. Not even the refinements of modern warfare are capable of slowing down the present rates of increase of

world population. At the Vevey symposium, the statement was made that even if an atomic war were to destroy 200,000,000 people, that number would be replenished within five years at the present rate of increase of approximately 40,000,000 per annum. It would seem that the danger of atomic warfare is not so much the direct destruction of man as the destruction of the world-wide economic and political organization which is his only hope of keeping the increase of food supplies comparable with the increase in population.

A physician is entitled to ask the foregoing questions, but cannot be regarded as particularly competent to answer them. It is reasonable, however, to point out that the decade 1960, perhaps with one or two succeeding decades, constitutes a critical period. "Death control" has been immediately and widely applied. The necessary restriction of population increase, for reasons which have been discussed above, and because it involves personal decision and action, is likely to be very much slower in its application even when its inevitability is generally accepted. A favourable answer to the problems posed requires faith in the capacity of man to rise above the purely animal instincts in his nature and to achieve his intellectual and spiritual destiny.

Nutrition Education in the Medical School and Hospital

A proper basis in nutritional science should be given to the medical student in his pre-clinical years through the departments of physiology, biochemistry and pathological chemistry. It is important that the scientific grounding should be adequate, whether it is possible or not in the courses mentioned to emphasize or illustrate the clinical applications. The latter emphasis will depend upon the availability of staff with practical experience of the applications of nutritional science to man and to clinical medicine. If such staff are not available, illustrative clinics can be provided periodically through the clinical departments.

In the clinical years the systematic aspects of the application of nutritional science to clinical and preventive medicine should be continued through the departments of clinical medicine, chemical pathology and preventive medicine (or equivalent departments or sub-departments of promotive medicine, public health and hygiene and/or social medicine). But the major incentive to human and clinical application should come through the teachers of clinical medicine who should regularly emphasize the role of malnutrition or undernutrition in aetiology, methods of clinical recognition and assessment, the application and interpretation of biochemical tests,

and the role of diet in treatment and rehabilitation. These aspects should be stressed in both out-patient and in-patient teaching. Therapeutic dietetics should be taught in general outline by clinical teachers, but the detailed application should be covered and illustrated by dietitians. It is doubtful whether the practising doctor will ever have sufficient time to discuss the detail of diets with his patients. Dietitians are trained for this purpose.⁴²

The emphasis of applied human nutrition will vary with the stage of development of the country. In underdeveloped countries the importance of undernutrition and malnutrition are constantly emphasized in the clinical material attending out-patient departments and admitted to hospital. The relevance of nutrition will never be in doubt. The danger in clinical teaching is to take it for granted because it is so prevalent, and because the availability of good food and the media of nutrition education seem to be so slow in developing. The clinician is apt to shrug his shoulders and say "What can I do about this? I must practice medicine within the limitations of prevalent undernutrition and malnutrition". His voice must continually be raised in student teaching so that the prevalence and adverse significance of malnutrition and undernutrition are put before the student every day. In this way a climate of opinion is achieved among the medical profession and eventually communicated to the public and to administrators. In tropical underdeveloped countries, the importance of these principles is even greater. Reference is made in Chs. 7 and 14 to the extent to which, in the past, many diseases have been attributed to tropical parasites because they occur in tropical regions. This error has arisen from traditional dependence upon the idea of a single cause for disease. The growing appreciation of multiple ætiology in constitutional, chronic and degenerative diseases has helped to underline the importance of malnutrition as a contributory cause in a very large number of diseases. In particular, it is now appreciated that many diseases which occur in the tropics and which were previously thought of as tropical diseases occur also in underdeveloped regions outside the tropical belt. The study of these diseases in such regions has brought out the fact that if tropical parasites play any part in their ætiology it is only contributory and that often malnutrition is more important as a cause.

In developed countries, the relevance of malnutrition to medical practice was less obvious and was largely missed until the 1950s. It is, however, the principal theme of this book that the long-term effects of malnutrition, acting through the modification of constitu-

tion, are of great relevance to a variety of diseases of multiple and uncertain aetiology. If this opinion is correct, it becomes essential that nutrition be taken more seriously in medical education. The comparative neglect of this field of study both in medical education and in medical practice has been described.⁴² This neglect has been contrasted with the great activity which has gone into research in veterinary nutrition over many decades. The protein and fat decade (1950-60, Ch. 2) has been responsible for a reawakening of interest in human nutrition.

Some Thoughts for the Future

We are at the end of a protein decade, in the midst of a fat decade (1956-65) and probably commencing a carbohydrate decade. In Ch. 2 the complex constitution of these three groups of foodstuffs as sources of calories, tissue, vitamins, minerals and perhaps unidentified nutrients was examined. Vitamins, the original focus of interest in nutrition, have been temporarily displaced to the rear of the clinical stage, but will undoubtedly continue to yield fresh secrets in intermediary metabolism. For a few decades their use in clinical practice has often degenerated into quackery. Let us hope that a rational perspective will be restored to the temporary use of vitamins in supplementation of inadequate diets.

In Ch. 1 it was suggested that the application of new knowledge in scientific nutrition might prove disconcerting through a temporary revival of food quackery. This suggestion is made for the following reasons:

(1) Although man is omniverous it is increasingly apparent that his constitution is shaped in part by his habitual dietary patterns (Fig. 1).

(2) Many of his most troublesome diseases are of multiple aetiology and based on his constitution; his habitual dietary pattern is therefore very relevant to consideration of their prevention.

(3) Urbanization is leading to greater and greater dependence upon processed foodstuffs with resultant hazards from food additives and residues (Ch. 10) and change in their constitution, e.g. hydrogenation of fats (Chs. 8 and 19).

It is therefore not surprising to see a revival of "back-to-nature" food faddism. Up to a point this trend may be healthy if it leads to simplification of highly sophisticated and luxury diets. But it becomes unrealistic when it becomes "faddist". The modern urban dweller cannot get fresh fruits and vegetables regularly—indeed

frozen and canned products are usually of better quality and nutritive value than he can find among the faded and contaminated contents of retail market tables. While housewives increasingly hold paid employment the initiative of the food industry in taking many of her chores into the food factory is irresistible. There is no reason why processed foodstuffs should not be as healthy as natural foodstuffs if nutritional science provides the necessary information.

Healthy simplification of diets is to be encouraged; food faddism does not need to be opposed—it often keeps a neurotic happy! This should always be an aid to the medical practitioner, and there is no need to knock the neurotic's dietary props out from under him. The pressures of the healthy-minded members of his family will eventually achieve modification of his diet.

In the meantime, let us acknowledge that orthodox medicine has neglected the role of dietetics in the promotion of health and prevention of disease. In the face of cycles of enthusiasm for one or other cult of the "back to Nature" food faddists, we have resolutely emphasized the adaptability of man to diet. Man is undoubtedly adaptable to a great variety of diets; but almost certainly he has paid a penalty for some of his adaptations.

There are doubtless some lessons to be learnt from the history of man's civilization. In the early hunting and pastoral days he lived largely on animal and naturally growing vegetable products. When he became more settled, he started the agricultural production of staple carbohydrates. Under conditions of population pressure or where the production of milk was difficult, as in the tropics, he weaned his babies on to starchy paps and gave them mehl-nahrschaden or kwashiorkor. The Bushmen of the Okavango River in southern Africa, who are Stone Age hunters without any agriculture, feed their post-weaning children on a pap prepared from wild legumes and do not have kwashiorkor. But when man advanced again from the starchy paps to the use of cow's milk as a post-weaning food, did he lay early foundations for atheroma? Have we to choose between cirrhosis and primary liver carcinoma on the one hand and the results, on the other hand, of atherosclerosis in our middle to later years?

During the decade just completed the dangers of obesity have been abundantly confirmed, but its pathogenesis remains a mystery (Ch. 14). There is still a fortunate majority who can dispose of excess calories with impunity and an unfortunate minority who have to count every calorie. Fortunately the pseudo-scientific theory that exercise is of no value in preventing obesity is yielding to common

sense. It can be hoped that in the coming decade a physiological explanation may be found for what is obviously an inherited tendency to deposit unneeded calories in adipose depots instead of dissipating them as heat.

The same decade has seen an increasing awareness of the possible dangers of over-consumption of certain foodstuffs or nutrients. This is well illustrated in questions which are being asked about diets containing 40–45 per cent of calories from fat (Chs. 8 and 19) and about the desirability of 0·8 g. as a recommended allowance of calcium for an adult. This figure, part of the American cult of plenty,⁴² and its effects on dietitians and dietetic education has been discussed in Ch. 25.

We must ask whether omnivorous man is adaptable to a variety of diets. The answer from history and geography is "Of course". But is there an optimum diet on which he achieves his best performance? What do we mean by "best performance"? Is it in the physical, intellectual, or spiritual realm? What is the health that we are trying to achieve? Is it longevity, usefulness, or happiness?

Every veterinarian and farmer, when his animals lose condition, looks first to their diet. Doctors and laymen do the same for their pets. Every horse-trainer or rider knows the effect of oats on his horse. Why do oats increase the horse's friskiness and will-to-go? Is it that they improve nutrition? If so, was the basic diet sub-optimal, or is this state of friskiness undesirable as a permanent state? Is it that oats act by suggestion? If so, who is suggestible, the horse or the trainer? What lessons applicable to man can we learn from the horse and his oats?

Perhaps the cult of moderation in eating (not to mention other pleasures) may have material advantages in health and longevity which outweigh its alleged penalty of smugness.

The most important advance pending is clarification of the mechanisms discussed in Ch. 4, through which man's constitution, and therefore his experience of many diseases of uncertain and multiple ætiology, including the important degenerative diseases are in part determined. Our knowledge of these mechanisms is at present rudimentary. The subject is due for intensive investigation.

CHAPTER 17

References

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CHAPTER 18

THE FIFTH INTERNATIONAL CONGRESS ON NUTRITION

THIS congress, the fifth in a series held each third year, took place in Washington D.C., U.S.A., in September 1960. The manuscript of this book was already in proof, but arrangements had been made with the publishers to bring it right up to date by adding this chapter as an addendum. The programme of the Congress was wide enough to cover almost the whole field of nutrition. There were about 2,000 registrants, 367 papers were communicated in abstract, and subjects of broad general interest were covered by 7 panel meetings, and 2 plenary sessions. The titles of papers communicated and the contributors' names in the 7 panel sessions are listed here as they constitute a guide to international interest and scope in the various fields of nutrition.

PANEL I—EVALUATION OF NUTRITIONAL STATUS IN MAN

Chairman: Grace A. Goldsmith, U.S.A.

Moderator: E. W. McHenry, Canada

Interpretation of Nutritional Requirements in Terms of Action Programs. E. W. McHenry, *School of Hygiene, University of Toronto, Toronto, Canada.*

Sampling, Organization and General Plan for the Evaluation of Nutritional Status in Man. A. E. Schaefer, *Interdepartmental Committee on Nutrition for National Defense, National Institutes of Health, Bethesda, Maryland, U.S.A.*

Public Health Indices of the Nutritional Status in Man. C. den Hartog, *Voorlichtingsbureau voor de Voeding, The Hague, The Netherlands.*

Clinical Evaluation of Calorie and Protein Status. H. W. Bansi, *General Hospital, St. Georg, Hamburg, Germany.*

Clinical Evaluation of Vitamin and Mineral Status in Man. M. V. Radhakrishna Rao, *Department of Nutrition, Government of Bombay, Haffkine Institute, Bombay, India.*

Biochemical Evaluation of Nutritional Status in Man. Guillermo Arroyave, *Institute of Nutrition of Central America and Panama, Guatemala City, Guatemala.*

Dietary Determination of Nutritional Status. Dorothy F. Hollingsworth, *Food Science and Atomic Energy Division, Ministry of Agriculture, Fisheries and Food, London, England.*

PANEL II—PROTEINS AND AMINO ACIDS IN NUTRITION

Chairman: Eliane Le Breton, France

Moderator: John F. Brock, South Africa

Dietary Proteins in Relation to Man's Health. John F. Brock, *Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.*

The Ideal Aminogram. James B. Allison, *Bureau of Biological Research, Rutgers, The State University, New Brunswick, New Jersey, U.S.A.*

Biochemistry of Human Protein Metabolism. V. N. Patwardhan, *Nutritional Research Laboratories, Indian Council of Medical Research, Andhra Pradesh, India.*

Vegetable Protein Mixtures for Human Consumption. N. S. Scrimshaw and R. Bressani, *Institute of Nutrition of Central America and Panama, Guatemala City, Guatemala.*

Valeur Proteique de l'Alimentation dans les Pays Tropicaux et Sub-Tropicaux. M. Autret, *Nutrition Division, Food and Agriculture Organization, Rome, Italy,* and R. Jacquot, *Centre National de la Recherche Scientifique, Bellevue, France.*

Some Aspects of Protein Malnutrition in Childhood. Silvestre Frenk, *Department of Nutrition and Endocrinology. Hospital Infantil de México, México, D.F., Mexico.*

Adult Protein Requirements. Hisato Yoshimura, *Department of Physiology, Kyoto Prefectural University of Medicine, Kyoto, Japan.*

PANEL III—LIPIDS IN HEALTH AND DISEASE

Chairman: Ancel Keys, U.S.A.

Moderator: K. Lang, Germany

Stoffwechsel der Lipide. K. Lang, *Physiologisch-Chemisches Institut, Johannes Gutenberg Universität, Mainz, Germany.*

Metabolism of Bile Acids. Sune Bergström, *Karolinska Institutet, Stockholm, Sweden.*

Lipids and Atherosclerosis. B. Bronte-Stewart, *Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.*

Pathology of Lipid Disorders: Liver and Cardiovascular System. W. Stanley Hartroft, *Department of Pathology, Washington University School of Medicine, St. Louis, Missouri, U.S.A.*

The Role of Lipids in Normal Metabolism. A. C. Frazer, *Department of Medical Biochemistry and Pharmacology, University of Birmingham, England.*

Endocrines in Lipid Metabolism. G. S. Boyd, *Department of Biochemistry, University of Edinburgh, Scotland.*

PANEL IV—NUTRITION IN MATERNAL AND INFANT FEEDING

Chairman: Icie Macy Hoobler, U.S.A.

Moderator: F. W. Clements, Australia

Nutrition in Maternal and Infant Feeding (Some broad general issues for possible discussion). F. W. Clements, *Institute of Child Health, University, Sydney, Australia.*

Orientation in Infant Feeding. Paul György, *Department of Pediatrics, University of Pennsylvania and Philadelphia General Hospital, Philadelphia, Pennsylvania, U.S.A.*

Nutrition and Lactation. C. Gopalan and Bhavani Belavady, *Nutrition Research Laboratories, Indian Council of Medical Research, Hyderabad-7, India.*

Cultural and Anthropological Factors in Infant and Maternal Nutrition. Derrick B. Jelliffe and F. John Bennett, *Department of Paediatrics and Preventive Medicine, Makerere College Medical School, Kampala, Uganda.*

Digestion in Infancy. B. S. Platt, *Medical Research Council and Department of Human Nutrition, London School of Hygiene and Tropical Medicine, London, England.*

Nutritional and Physiological Adaptations in Pregnancy. George H. Beaton, *School of Hygiene, University of Toronto, Toronto, Ontario, Canada.*

Nitrogenous Constituents of the Urine in Kwashiorkor. R. F. A. Dean, *Medical Research Council, Mulago Hospital, Kampala, Uganda.*

PANEL V—EFFECTS OF PROCESSING AND
ADDITIVES ON FOODS

Chairman: C. A. Elvehjem, U.S.A.

Moderator: W. J. Darby, U.S.A.

Nutritional Effects on Milk of Chemical Additives and Processing. S. K. Kon, *National Institute for Research in Dairying, Shinfield, Reading, England.*

Nutritional Aspects of Processing and Chemical Additives on Fats and Oils. J. P. K. van der Steur, *Unilever N. V., Rotterdam, The Netherlands.*

Modern Technology as Related to the Safety of Foods. Bernard L. Oser, *Food and Drug Research Laboratories, Inc., New York, New York, U.S.A.*

Nutritional Aspects of Pesticides and the Use of Agricultural Chemicals. Simone Dormal, *Centre de Recherches de Phytopharmacie, Gembloux, Belgium.*

Einfluss der Verarbeitung in Industrie und Haushalt auf den Nährwert von Fleisch, Getreideprodukten und Hulsenerfrüchten. H. D. Cremer and W. Büttner, *Institut für Ernährungswissenschaft der Justus Liebig-Universität, Giessen, Germany.*

Nutritional Aspects of the Use of Spices and Flavourings. B. Mukerji, *Central Drug Research Institute, Lucknow, India.*

Nutritional Aspects of the Use of Food Colors. Ross A. Chapman, *Food and Drug Directorate, Tunney's Pasture, Ottawa, Canada.*

PANEL VI—ANIMAL NUTRITION AND FOOD
PRODUCTION

Chairman: L. A. Maynard, U.S.A.

Moderator: D. P. Cuthbertson, Scotland

Problems of Animal Nutrition in Underdeveloped Areas. E. J. Bigwood, *Department of Biochemistry and Nutrition, Faculty of Medicine, Brussels University, Belgium.*

Efficiency of Feed Conversion by Different Classes of Livestock in Relation to Food Production. K. L. Blaxter, *The Hannah Dairy Research Institute, Kirkhill, Ayr, Scotland.*

Relation of Nutrition of the Young Animal to Subsequent Fertility and Lactation. Knut Breirem, Asmund Ekern and Thor Homb, *Institute of Animal Nutrition, The Agricultural College of Norway, Ballebekk, Norway.*

Recognition and Correction of Deficiency States. E. J. Underwood, *Institute of Agriculture, University of Western Australia, Nedlands, Australia.*

Quality and Quantity of Final Products Other than Milk—Ruminants. Jürgen Tiews, *Institute of Physiology and Animal Nutrition, University of Munich, Germany.*

Quality and Quantity of Final Products Other than Milk—Non-Ruminants (Pigs). Hjalmer Clausen and Jørgen Ludvigsen, *National Research Institute on Animal Husbandry, Copenhagen, Denmark.*

Quality and Quantity of Final Products—Poultry. Gerald F. Combs, *Department of Poultry Husbandry, University of Maryland, College Park, Maryland, U.S.A.*

PANEL VII—THREE HOURS AROUND THE WORLD:
NEW POSSIBILITIES IN NUTRITION RESEARCH

Chairman: W. H. Griffith, U.S.A.

Moderator: V. Ramalingaswami, India

Nutritional Aspects of Calculus Disease of the Urinary Tract. V. Ramalingaswami and A. L. Aurora, *Department of Pathology, All-India Institute of Medical Sciences, New Delhi, India.*

Classical Deficiency Diseases. Robert R. Williams, *Summit, New Jersey, U.S.A.*

Some Aspects of the Nutrition and Physique of Bantu Communities. Alexander R. P. Walker, *Council for Scientific and Industrial Research and the South African Institute for Medical Research, Johannesburg, South Africa.*

Malabsorption Syndrome. J. H. van de Kamer and H. A. Weijers, *Central Institute for Nutrition and Food Research T. N. O., Utrecht, The Netherlands.*

Neuromuscular Disease in Relation to Nutrition. Eric K. Cruikshank, *University College of the West Indies, Kingston, Jamaica.*

Action of Grain Affected by Microscopic Fungi on Human Health. Julia I. Rubenstein, *Academy of Medical Science, Moscow, U.S.S.R.*

Nutritional Aspects of Cirrhosis and Carcinoma of the Liver. Gerrit Bras, *Department of Pathology, University College of the West Indies, Kingston, Jamaica.*

Panel papers were reprinted for those attending the congress and are to be published in Federation Proceedings, together with an abstract of the discussion which formed the main part of each panel meeting.

It will be possible here to comment only on some highlights of the wealth of material presented.

All sources of this chapter will be found in the official programme, abstracts or panel brochures of the Congress. Many of them will not be published until well into 1961. Until they appear the writer of this chapter must take responsibility for interpretation (or misinterpretation) of many views expressed in official and unofficial discussion and not susceptible to detailed checking at the time of writing. For this reason the names of individual workers are in the main omitted.

Lipids in Health and Disease. The hypothesis that ischaemic heart disease is increasing in prevalence among the more privileged population groups of the world mainly because of change in the quantity and quality of dietary fat has stimulated a great deal of work in the fields of lipid metabolism, of blood clotting and of research into atherosclerosis in general. Whether the hypothesis is, or is not, finally accepted there can be no doubt of its stimulating and fertilizing value in the fields mentioned. The panel on *Lipids in Health and Disease* brought together and summarized some new approaches and concepts. On the hypothesis itself the summarizer took a view very similar to that expressed in Chapters 8 and 19. While adhering to a cautious approach to the likelihood of causality in statistical correlations between diet and ischaemic heart disease it was allowed that the individual at risk might reasonably try to improve his expectation of life and health by restricting the quantity of dietary fat and substituting the less saturated vegetable origin fats for some of the more saturated fats of animal or industrial origin. It was allowed that a similar dietary trend might be encouraged among privileged groups on a common-sense basis, without attempting a formal revision of recommended allowances at the present stage of our knowledge. The incompleteness of present knowledge of the relationships between lipid metabolism and such parameters as chain length and degree of unsaturation of fatty acids and the alterations in saturation and isomerization resulting from the industrial processes of the fat food industry was stressed.

The physiology of fat absorption and the role of intestinal bacteria in reciprocal relations between bile acid and lipid metabolism were reviewed.

The role of the endocrine glands in lipid metabolism gave rise to lively debate. The applicability of endocrine therapy to the control of ischaemic heart disease through lipid metabolism or other mechanisms appears, however, at present to be discouraging.

Œstrogen therapy in particular seems to carry more disadvantages than benefits.

With regard to atheroma and atherosclerosis in general, the mood of the medical profession has shifted in the last decade from helplessness to one of guarded optimism that this may be in part a preventable disease. The problem is recognized to be immensely complex and it is accepted that ætiology must certainly be multiple. Even when allowing, however, for largely or wholly uncontrollable factors of inheritance and hæmodynamic wear and tear, there is room for hope in the obvious association with diseases characterized by hyperlipidæmia and hypercholesterolæmia. If lipid metabolism and the ways in which it is affected by diet can be elucidated, there is no lack of logic in postulating that atheroma and its sequelæ may be in part preventable. Certainly the hypothesis has stimulated fertile research. Rats and mice as experimental animals will almost certainly yield conclusions supplementary to and perhaps corrective of those derived from work on herbivorous rabbits. A growing volume of work on primates must give valuable results.

It is fair, then, to say that the Fifth International Congress for Nutrition endorsed the hopes expressed in Chapters 8 and 19 that the last decade has seen an important change in attitude towards the possibility of progress in knowledge towards an understanding of the ætiology and pathogenesis of atherosclerosis in general and of ischæmic heart disease in particular; further, that among an admittedly complex and multiple ætiology the effect of diet in general and of quantity and quality of dietary lipids must be regarded as worthy of immediate and intensive study. This progress undoubtedly encourages hopes for prevention at least of the steadily increasing toll of mortality and morbidity from ischæmic heart disease.

Proteins and Amino Acids. A conference on *Protein Needs* was sponsored by the Committee on Protein Malnutrition of the Food and Nutrition Board of the National Academy of Sciences—National Research Council of the U.S.A. It was held in Washington a few days before the International Congress, and the proceedings will be published in full by the National Research Council.

Many of the highlights of this conference were included in the papers and discussion at the Panel on Proteins and Amino-acids at the subsequent Congress. They include the following:

The conference was concerned particularly with the extent to which expensive proteins of animal origin could be conserved by the use of proteins of vegetable origin mixed in such combinations that the amino-acid deficiencies of one are compensated for by relative

abundance in another. Combinations of cereals and legumes, for example, often fulfil this requirement. In order to solve this problem it is necessary to know more about:

- (1) Differences in metabolism between proteins of high and low biological value, or between proteins of animal or vegetable origin;
- (2) Methods of measuring the adequacy and extent of protein or amino-acid reserves in the body; and
- (3) Dependent on answers to 1 and 2, the minimum requirement of mixed proteins of different biological values under varying physiological conditions.

As recorded in Chapter 7, the FAO Report on Protein Requirements has outlined the problem but was unable to answer these questions and had to make only very tentative recommendations.

Discussion of nitrogen balance on predominantly vegetable diets led to a radical reappraisal of certain aspects of the physiology and biochemistry of protein metabolism. Patwardhan reviewed evidence produced by his own and other groups in India that change in quality of protein from predominantly vegetable to predominantly animal sources at isonitrogenous levels leads to a very substantial increase in urinary nitrogen. This change appeared not to be attributable to better digestibility of the animal protein because differences in faecal nitrogen were small. The consequential more strongly positive nitrogen balance on vegetable protein was not reflected in weight gain.

The conference was reminded of the report published in 1954 by Holmes *et al.*, showing large and long-continued nitrogen retention in adult males in Uganda which were not reflected in corresponding weight gains. Discussion centred on the possibility of systematic error in nitrogen balance techniques. Such an error would need to apply only to the vegetable diets. One possibility is incomplete recovery of faecal nitrogen, since vegetable diets are known to be very resistant to Kjeldahl digestion. It was agreed that unmeasured loss through sweating could not explain the differences shown between predominantly vegetable- and predominantly animal-source diets in these experiments. Another interesting aspect of the findings was confirmation of an older observation of high percentages of unidentified constituents in total nitrogen in the urine of subjects consuming predominantly vegetable diets. This percentage fell towards conventional levels when the subjects were fed predominantly animal protein diets, suggesting that the high figures result

from the quality of dietary protein and do not indicate permanently abnormal nitrogen metabolism or renal function in Indian subjects as had earlier been suggested. Among the many possible constituents of undetermined urinary nitrogen, interest centred in purine and pyrimidine bases and Dean reported progress towards their identification. He also reported high figures for percentage unidentified urinary nitrogen in kwashiorkor in relapse; these high figures fell within 4 or 5 days of effective treatment.

Patwardhan drew attention to the pioneer studies of Folin in 1905 and confirmed Folin's view that it is the level of total urinary nitrogen, rather than the source of dietary protein, which determines the level of urinary urea.

These observations suggest strongly that the physiology of nitrogen metabolism and excretion may be due for a major overhaul in the light of experience with vegetarian diets.

Very little progress was reported in the problem of assessing the nature and extent of protein reserves. Existing knowledge is reviewed in Chapter 7 and virtually nothing can be added arising from the Conference or Congress. Studies at present being carried out with isotopes or tritium on animals will need to be applied to man, as and when this is possible, in order to define the changes which occur in body compartments in malnutrition (see Chapter 20). This may clarify the difficult problem of the "Labile Protein Pool" and its relations to fixed tissue nitrogen. The concept of a "pool" will probably give way to varying contributions to emergency protein needs from a range of tissues of descending rate of protein turnover.

It follows, then, that no further progress has been made in defining protein requirements. It is clear, however, that mixed proteins of remarkably good combined biological value can be created by mixing several proteins of vegetable origin. This principle is best exemplified in Incaparina (referred to in Chapter 21) (prepared by the Institute for Nutrition for the Central Americas and Panama).

If this should prove to have less than optimum nutritive value for man then it is clear that quite small additions of animal protein will enhance its nutritive value greatly. J. D. L. Hansen has shown, for instance, that whereas a mixture of maize and pea flour has good nutritive value for infants only at high intakes, the addition of 10 per cent or 17 per cent respectively of skimmed milk or fish flour will give it a nutritive value equal to that of skimmed milk at quite reasonably low intakes. As mentioned in Chapter 7 it appears

that protein quality can only be defined in relation to a fixed quantity, and that the practical limitation on the nutritive value of proteins of vegetable origin lies mainly in the uncomfortably large quantities which have to be consumed.

The method described in Chapter 28 of expressing the nutritive value of a diet containing proteins of several sources as "Net Dietary Protein Value" promises well for future studies.

Nutrition in Maternal and Infant Feeding. The Panel under this heading provided a vindication of common-sense as the greatest of the senses as a scientific tool. Although there was in a sense nothing new nor anything which has not been covered by Chapters 12 and 24, it is worthwhile to comment on this excellent session. Although it appears to be difficult to do clinically demonstrable harm by feeding an infant a variety of formulæ which contain estimated requirements of nutrients, such aphorisms as "Human milk is for infants and cow's milk is for calves", and "Maximal infant growth is not necessarily optimum growth" are refreshing in this scientific era. The Panel discussion was summarized by pointing to the need for further information on: (1) the nutritive value of human milk as estimated perhaps in primate growth studies; (2) the late effects of early feeding (Chapter 14); and (3) rate of maturation in relation to diet.

**INVITED CONTRIBUTIONS ON SPECIAL
SUBJECTS**

CHAPTER 19

DIETARY FATS

by

B. BRONTE-STEWART

DURING the last decade a great deal of interest has been focused on the role of dietary fats in clinical nutrition. The inclusion of fat in one's diet serves several purposes: (1) fats supply more than twice the number of calories than are available from equivalent amounts of protein or carbohydrate and this, with their lower water content, reduces the bulk of the diet; (2) fats prolong gastric emptying time and are absorbed at a slower rate than carbohydrates and in this way they probably increase the "staying power" of a ration and prevent a hunger reaction; (3) fats are essential for the palatability of food-stuffs, as anyone who has been on a low-fat diet, or has suffered the severe rationing of the war period will testify; (4) dietary fats are important for the fat-soluble vitamins (A, D, E, and K) contained therein, and possibly contain essential nutrients (*see below*).

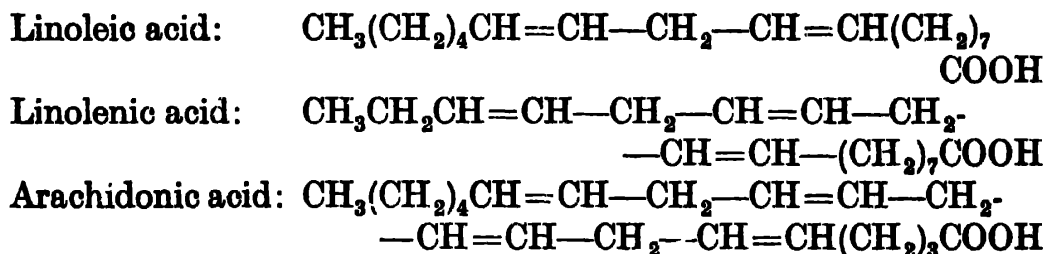
If these vitamins could have been supplied in another form, and provided that sufficient carbohydrate and protein were given for energy purposes, fats were held to have a non-vital role in human health. The term "empty" calories grew out of this concept. Many examples to illustrate this non-vital role became apparent, as epidemiologists became aware of the differing dietary patterns of the different races in the world. By far the greater proportion of the world's population, especially in Asia and Africa were living, thriving and procreating on diets with a very low fat content. In Japan for example, the mean percentage of calories derived from fat was only about 10 per cent, which would mean that some of the population would have been consuming throughout life a diet extremely low in fat content. On these premises one may justifiably question whether dietary fat is an essential nutrient or merely a less bulky alternative to carbohydrate for the supply of calories.

Prior to 1950 there was little to indicate in man that health was adversely affected by a deficiency of or an excess of fat in the diet. It was well known that an unduly high proportion of fat could give rise to ketosis and, indeed, such was used therapeutically. In the animal,

however, inclusion of fat in the diet was shown to increase the efficiency of the performance of such physiological functions as growth, sexual maturation, pregnancy, lactation, work capacity, length of survival during subsequent fasting and nitrogen metabolism.²⁰

The Essential Fatty Acids

More than 30 years ago, Evans and Burr²³ found that rats failed to thrive on a fat-free diet. When fat was added the rats gained weight again and the various lesions that were seen disappeared. The classical experiments of Burr and Burr^{15, 16} revealed that the active principle was found in those unsaturated fatty acids containing more than one double bond, the polyunsaturated fatty acids. The common polyunsaturated acids are all straight long-chain fatty acids, having two to six double bonds separated by single $\text{—CH}_2\text{—}$ groups. The most important acids of the group are:



Not all the polyunsaturated fatty acids had this biological activity, and those that had differed in degree. The most active were linoleic acid and arachidonic acid but later it was shown that the latter could be synthesized from the former; for this synthesis pyridoxine was necessary.⁶⁴ Conjugated and cis trans forms were unable to cure the deficiency syndrome. In fact it was possible that they behaved as metabolic antagonists to the normally occurring cis-cis acids.³⁰ It is now recognized that part, if not all of the deficiency syndrome can be cured by any fatty acid possessing a double bond at the sixth carbon position counting from the terminal methyl group. As these acids cannot be synthesized—at least to a sufficient degree—they became known as “Essential Fatty Acids” (EFA) and for a while were regarded as vitamin F. EFA deficiency has since been produced in a wide variety of animals: rats, mice, dogs, guinea pigs, pigs, chicks, sheep, calves, monkeys, insects and meal worms⁵⁷ and lately possibly in man.³⁷ The terms “essential fatty acids” and “polyunsaturated fatty acids” are not necessarily synonymous. Holman²⁸ suggests that the term “essential fatty acids” should be reserved only for those substances which are active both for growth and maintenance of

dermal integrity, limiting the term to linoleic and arachidonic acids and to such other acids as may be derived metabolically from them. On the other hand, as in amino-acid metabolism, one must recognize that fatty acids essential to the rat need not be identical to those essential to man. As they are essential for normal growth, effects are seen most easily in the post-weaning period of life. In the deficient state, widespread effects have been noted.

The EFA Deficiency Syndrome. The rigid exclusion of fat from the diet of young rats leads in about 70–90 days to retardation of growth and scaliness of the skin. The scaliness is seen particularly on the dorsum of the hind feet and on the tail, and may lead on to caudal necrosis. An increase in dandruff on the back of the rat occurs and the normal yellow-brown pigment of the rat's skin disappears. At this stage the skin becomes more permeable to water, and an increased consumption of water is seen without an increase in the volume of urine excreted. Hair may be lost from the face, back and throat. Finally the kidneys become affected and hæmaturia may be noticed before death. The dermal change is variable, being dependent on the relative humidity of the atmosphere in which the animals are kept. Other effects reported in the deficiency state are an increase in capillary permeability or lowered capillary resistance; an increased fragility of the red blood cell and degeneration of spermatogenic epithelium. EFA are necessary for normal reproduction and lactation; they exert a protective effect against the toxic features produced by x-irradiation injury; and they have a definite relationship to cholesterol and phospholipid metabolism.

In the experimental animal other beneficial effects of fat-containing diets have been shown, but here there is no positive evidence that the improvements are due to the EFA content of these fats. It has been shown, for example, that the period of survival of rats subjected to fasting is greatest when they received a high-fat diet during the pre-fast period than if they have been pre-fed with carbohydrate or protein. This has been ascribed to the sparing action of fat on liver glycogen and protein metabolism. Fat-fed animals have a slower rate of glucose utilization and a lower susceptibility to insulin. The phase of protein metabolism, responsive to fat is the nitrogen minimum, or the minimum level of urinary nitrogen produced on a protein-free diet. The lowest excretion of urinary nitrogen was seen in the group receiving a high-fat diet during the pre-fast period.²⁰

Biochemical Findings in EFA Deficiency. The characteristic finding whereby the deficiency can be recognized is a fall in the

dienoic (linoleate) and tetra-enoic acids accompanied by a rise in trienoic acids.²⁹ This rise in trienoic acid is the most striking chemical change and has been shown by Mead and Slaton⁴⁴ to be eicosatrienoic acid with its first double bond at the ninth carbon atom from the terminal methyl group. By its terminal structure therefore it could be synthesized from oleic acid to substitute partially for the lack of normal polyunsaturated acids or precursors which must be supplied in the diet.

These changes in polyunsaturated fatty acid composition take place several weeks before dermal symptoms appear. It is in the heart muscle lipids that these changes are reflected most dramatically. The lipids in the testis, liver, kidney and brain show a less marked change, but the changes are more consistent and greater than those seen in skin, adipose tissue and muscle.

Metabolic Functions of the EFA. A structural function for EFA is implied by the skin, red cell and capillary defects which are seen in the deficiency syndrome. EFA form part of cell membranes and are found in mitochondria possibly functioning by virtue of their easily oxidized, activated methylene groups, as active centres in enzymes.²⁹ An important function appears to be the regulation of cholesterol and fat metabolism. Cholesterol esters are composed of the more highly unsaturated fatty acids. In EFA deficiency typical fatty livers are seen. The liver cholesterol ester becomes more saturated and there is an increase of liver and adrenal cholesterol of considerable magnitude. This is possibly due to the fact that cholesterol cannot be transferred readily to other tissues from the liver in the absence of EFA. The onset of EFA deficiency may be accelerated by any method whereby the serum cholesterol is raised concomitantly. The deficiency syndrome may develop within a month on a fat-free diet in the presence of alloxan diabetes, or when thiouracil, cholesterol or other agents which induce hypercholesterolaemia are included in the diet. In attempts to maintain the plasma cholesterol ester fatty acids constant, the body stores of polyunsaturated fatty acids are depleted and thereby the onset of EFA deficiency is hastened.²⁹

The Requirement of EFA. In hypercholesterolaemic states an increased requirement of EFA would be expected. Similarly, the feeding of hydrogenated fat has accelerated the onset of the deficiency syndrome. This, with other data, suggests that no fixed requirement can be stated, but that the requirement is proportional to the total fat intake. A sex difference in requirement too is seen from the studies on x-irradiation effects on the deficiency state. Young female rats demonstrated a greater resistance to x-irradiation

than males, but no sex differences were apparent in the older rats.²⁰

The Role of EFA in Man. Isotopic studies in man³⁷ show that it is unlikely that EFA can be synthesized in any quantity. The deletion of EFA from the diet in the animal causes such drastic changes morphologically and metabolically in many organs in a wide variety of species that it would be surprising if these substances are not required by man. For these effects, however, there has to be a rigid exclusion of all EFA from the diet of the actively-growing animal and no dietary counterpart occurs in man. Nevertheless, there is evidence that an absolute deficiency state can be produced in man and there is much speculation on a possible relative deficiency state in disorders associated with hypercholesterolaemia.

Hansen *et al.*²⁷ fed synthetic fat-free diets to babies and reported that in over half of the infants who remained on this diet for at least one month, dryness and leather-like thickening of the skin occurred, followed by desquamation and frequently annoying exudation in the body folds. There was diarrhoea and a rash in the diaper region. On adding EFA to the diet there was a marked clinical improvement even within three weeks, the low values for the two and four double-bond fatty acids in the blood serum increased, while the high values for the three double-bond acids decreased. Tripalmitin, a saturated triglyceride, failed to produce any improvement after four weeks in one individual whose skin remained dry, thickened and scaly, with oozing in the body folds. Later, the milk mixture was changed to contain a liberal amount of linoleic acid with complete clearing of the skin condition within two weeks.

The skin lesions described above resemble somewhat the skin lesions seen in kwashiorkor in some areas. In most areas where kwashiorkor develops, the habitual consumption of fat, as well as of protein, is very low. Experimentally, fat has been shown to have a sparing action on the urinary minimum nitrogen and in kwashiorkor extensive fatty infiltration of the liver is a prominent feature. Schendel and Hansen⁵⁵ have shown marked changes in serum lipids during the recovery phase from kwashiorkor. There is a rise in serum cholesterol levels accompanied by a fall in the dienoic and a rise in the trienoic fatty acids; the latter resembling the biochemical findings of EFA deficiency. On the other hand, these changes may merely reflect transport phenomena occurring during the mobilization of the liver fat. Recently, however, a great deal of interest has been focused on reports suggesting that the addition of fat to the diet in addition to protein in the treatment phase accelerates recovery.¹⁹ The role of essential fatty acids, therefore, in kwashiorkor, has still to be fully evaluated.

In adults, apart from steatorrhœa and other malabsorption syndromes, there is no recognized clinical disorder that could be ascribed as being due to an absolute fat deficiency. As a required nutrient in the diet of adults, Osborne and Mendel's⁵⁰ opinion that the minimum necessary for nutrition must be exceedingly small, still seems true; it is certainly borne out by the many millions thriving and multiplying in Africa and Asia. On the other hand, there has recently been a rapid accumulation of reports suggesting that a relative deficiency of polyunsaturated fatty acids, relative to an increasing and excessive total fat intake, is related to certain human disorders, in particular ischæmic heart disease.

The Dietary Fat Hypothesis of Ischæmic Heart Disease

Apart from the acquirement of obesity from the excessive intake of calories, few, prior to 1950, would have accepted that other deleterious effects on health could be ascribed to an excessive intake of dietary fat. For nearly half a century, however,² it had been well known that feeding fats such as egg and bone marrow led to a sharp rise in the serum cholesterol levels and atherosclerosis in the experimental animal. As this could be reproduced with pure dietary cholesterol, it was felt that this was due to an excessive intake of cholesterol in the diet. For this and other reasons extrapolation of data in the experimental animal to man was not wholly acceptable.

At the turn of this present decade, however, there appeared two publications^{40, 58} to show that the sharp fall in death rate from circulatory disease during the 1939-45 war in many European countries was paralleled by fall in the consumption of milk, butter, cheese and eggs. In the countries not subjected to the deprivation of the war, the mortality from ischæmic heart disease continued to rise.

In 1952, Keys initiated a series of studies on races with wide differences in prevalence of ischæmic heart disease. By 1956³³ Keys was able to show that in areas where the proportion of calories consumed as fat was about or above 40 per cent, a high prevalence of ischæmic heart disease existed and the serum cholesterol levels rose sharply with age. In groups eating little fat such as South African Bantu, the Chimbu of New Guinea and the Japanese, ischæmic heart disease was rare and the rise of serum cholesterol level with age was insignificant.⁹

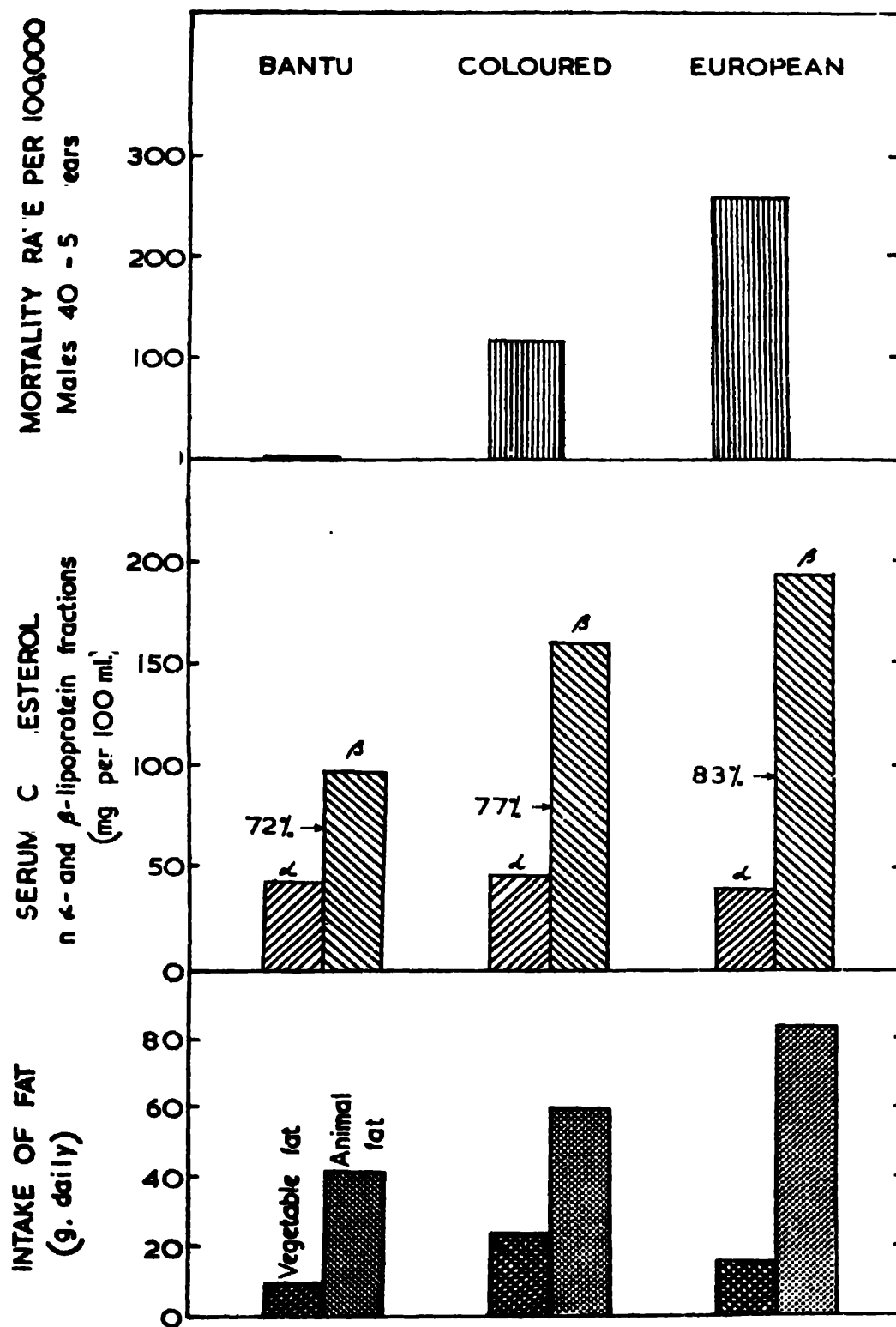
Epidemiological data need careful interpretation as genetic and many other environmental variables are at play and parallelism of trends need not indicate causal association. Although blood group studies¹⁴ reveal a higher prevalence of ischæmic heart disease in

group A individuals, it is unlikely that race in the genetic sense could account for these striking differences in prevalence as it is now known that ischaemic heart disease prevalence differs in the same race living under different environmental conditions. Firstly, it is far higher in Japanese who have emigrated and come under the influence of American mode of life in Hawaii and California than in those who have remained in Japan.³⁵ Differences in mean serum cholesterol levels and in dietary fat intakes run parallel. Toor and his associates⁶¹ record similar differences between early and recent Yemenite Jews in Israel. In England, the disease is nearly twice as common in the professional and executive classes as in the labouring classes. Prosperity rather than occupation appear to be the background to these social class differences as the same trend occurred in retired men and their wives over 65 years⁶³ while similar differences between rich and poor men in Madrid had been noted by Keys.³³ The amount of dairy products and other animal fats eaten constitutes one of the most important differences dependent upon social class with respect to the dietary habits of man.⁴⁶

Epidemiological studies carried out on the multi-racial community resident in Cape Town showed that certainly climatic conditions could not be responsible and added further confirmation to the triangular association that existed between ischaemic heart disease mortality, the level of the serum cholesterol and the dietary fat intake.¹¹ In all these races with widely divergent customs in modes of life and in the same race subjected to different environmental conditions, of the many environmental factors studied, only the dietary fat intake remains consistently in parallel with the mortality experience of this disease.

The emphasis was laid on the total fat intake and not, as in the experimental animal, on the dietary cholesterol intake. In support of the quantitative hypothesis was the fact that the increasing mortality from the disease in the U.S.A. could be explained by the fact that over the last 25 years the percentage of calories from fats had risen by 10 per cent to over 40 per cent,³¹ but no comparable rise had occurred in Great Britain. Further criticism of this hypothesis soon appeared. Frequent reference was made to the high fat consumption of the Eskimo and to the fact that despite similar total fat intakes, American and European mortalities were not alike. In fact the total fat intake in Denmark was higher than that of the U.S.A. but the mortality was only about a third as great.⁶³

Fat Quantity Versus Fat Quality. In the Cape Town survey, attention was paid to the nature of the dietary fat intake and it was



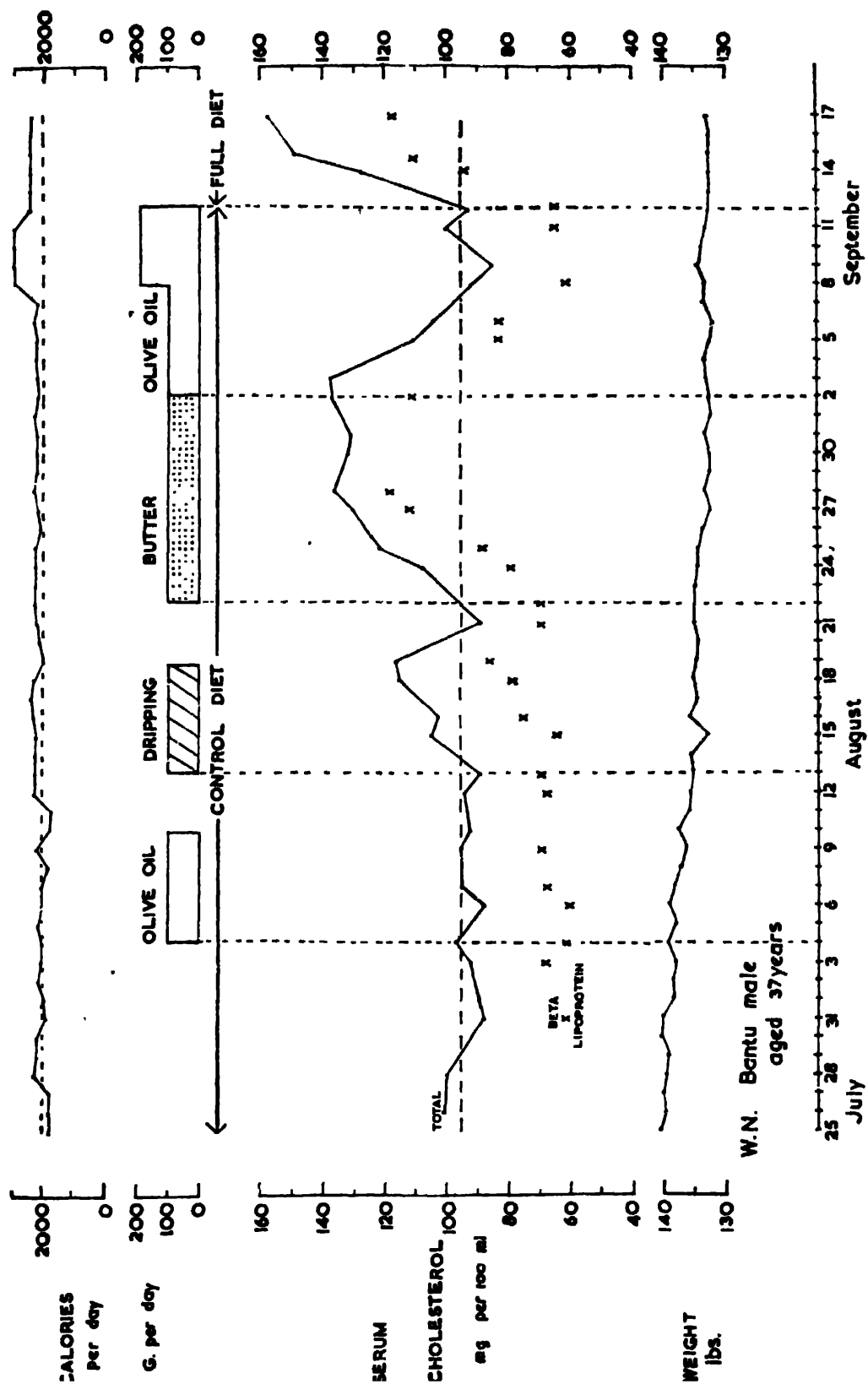
Based on Bronte-Stewart, Keys & Brock (1955).

FIG. 1. Mortality rates from ischaemic heart disease; the distribution of cholesterol throughout the lipoprotein fraction of the serum and the dietary fat intakes for males of similar age resident in the Cape Peninsula. The mean total cholesterol levels for Bantu, Coloured and European were 166 mg./100 ml., 204 mg./100 ml. and 234 mg./100 ml. respectively, and dietary fat intakes were 17 per cent, 25 per cent and 37 per cent.

revealed that the parallelism that existed between the mortality experience, the serum cholesterol trends and the diet could be attributed to the animal fat consumption. The vegetable fat intake showed no correlation whatever (see Fig. 1). Subsequently feeding experiments confirmed this under controlled conditions. They showed that as regards the effects on the serum cholesterol levels, dietary fats fell into two classes: animal and other hard fats elevated the levels while liquid vegetable and marine oils depressed them (see Figs. 2 and 3).¹²

Hydrogenation of these liquid oils abolished their ability to lower serum cholesterol levels, and tropical oils such as coconut and palm behaved as animal fats. The differences therefore lay in the constituent fatty acids, with those substances elevating serum cholesterol levels possessing a high content of saturated fatty acids while the serum cholesterol lowering substances contained a high proportion of polyunsaturated fatty acids. Hydrogenation destroys the most unsaturated fatty acids and any unsaturated acids that remain may lose their natural *cis-cis* configuration to become *trans* forms. Any essential fatty acid left then, would not be expected to have biological activity. Animal fats and tropical oils could be differentiated from those oils which lowered the serum levels by the paucity of essential fatty acids in the former. Furthermore the feeding of oils with a high content of essential fatty acids not only led to lower serum cholesterol levels than those seen on a low fat diet but led to a sharp rise in bile acid excretion, the end-product of cholesterol metabolism.²⁵ With their known effect on cholesterol metabolism in the animal, the conclusion drawn was that the essential fatty acids were accelerating turnover and increasing the elimination of cholesterol from the body. It was not unnatural therefore to view ischaemic heart disease as the algebraic product of time and a disordered fat metabolism resulting from a relative deficiency of essential fatty acids in the diet. The sex differences in requirement of EFA in the animal together with the other widespread effects noted, provided an attractive explanation for the sex difference in prevalence and the other features of ischaemic heart disease.

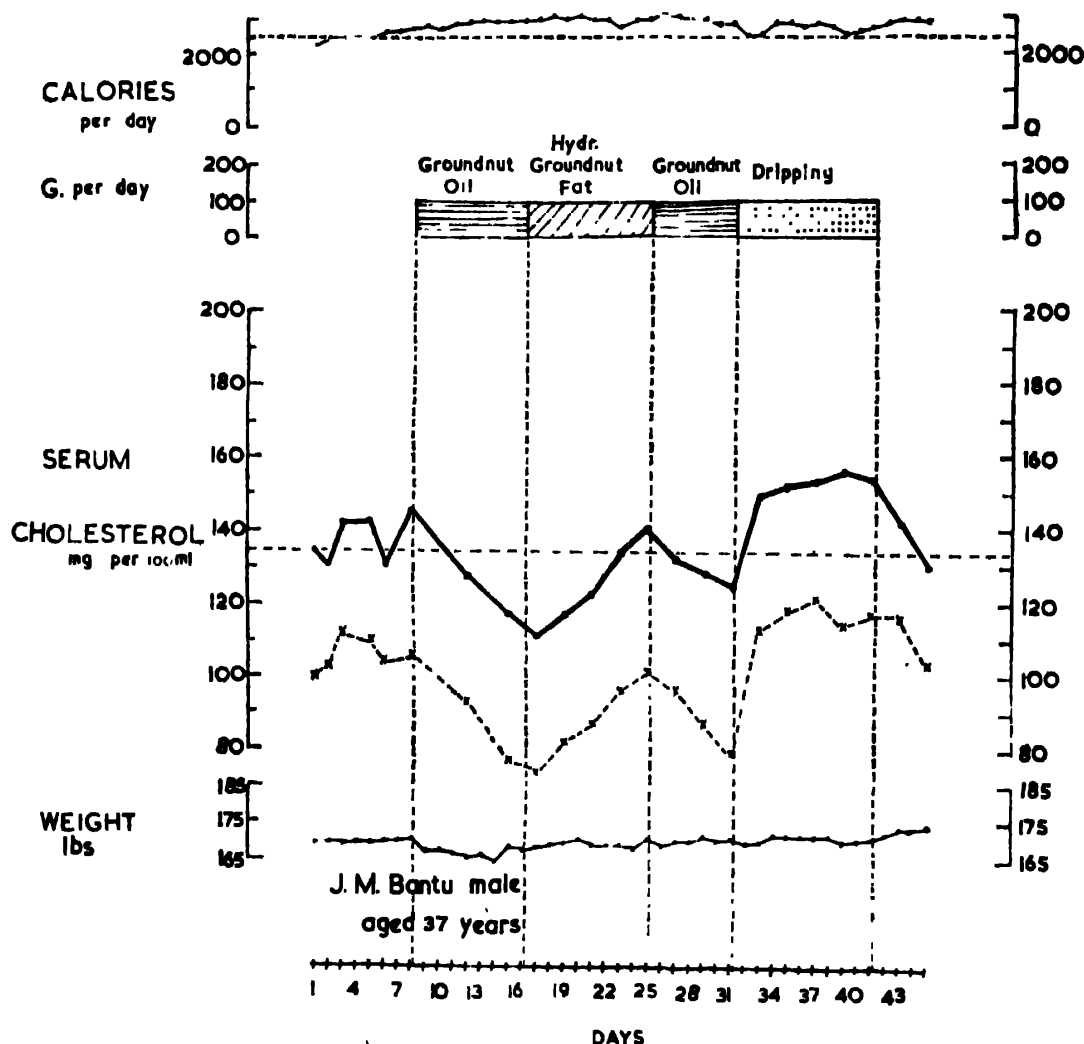
When one notes that at given age the American female dies more often than the Japanese male, and that the increasing mortality applies to female as much as to male,⁴² a factor in addition to the sex hormones must be at play. The male female sex ratio in prevalence of ischaemic heart disease is greater amongst the younger age groups and decreases with age. It is greatest too, in the more highly susceptible areas; areas where a great deal of fat is eaten.^{34, 43} A relative



Based on Bronte-Stewart, Antonis, Eales & Brock (1956).

FIG. 2. Olive-oil fails to elevate or maintain a raised serum cholesterol level. Beef-dripping, butter and beef-muscle (12th to 18th September) lead to immediate rises within 48 hours.

deficiency of EFA in the diet could be offered as the explanation, if one accepts that the requirement of EFA is proportional to the total fat intake and if one accepts that sex differences in requirement are seen only in young animals. Although in the Framingham study, dietary surveys have shown that males tend to eat more fat than

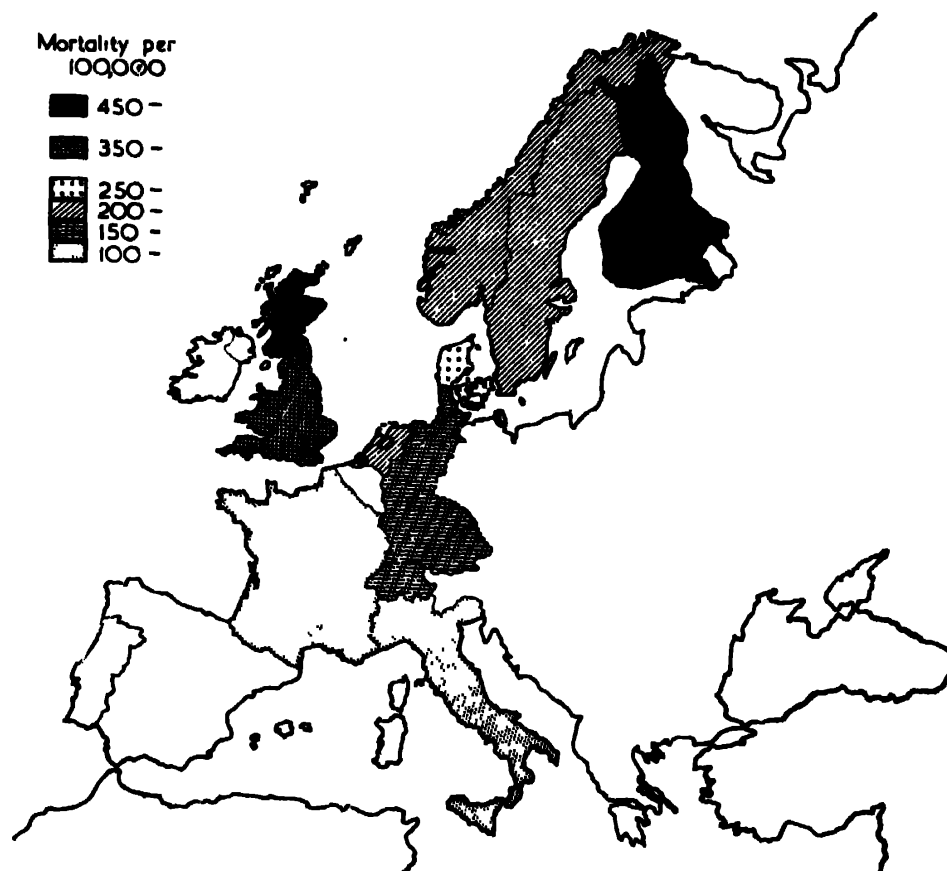


Based on Bronte-Stewart, Antonis, Eales & Brock (1956).

FIG. 3. The effect of hydrogenated ground-nut oil on the serum cholesterol level is quite different from that of the natural oil.

females⁴¹ it is Bersohn⁶ who has shown the first link between the nature of the dietary fat and the sex hormones. In long-term feeding studies on male prisoners, the urinary oestrodiol/cestriol ratio remains high on a diet where the fat content consists mainly of sunflower seed oil but falls to the low levels found in patients with ischaemic heart disease, when butter or hydrogenated fat is the source of the calories from fat.

This fatty acid imbalance theory suggests a solution to the question of the Eskimo with his high fat diet consisting largely of marine oils⁵⁸ but the Eskimo diet varies widely from area to area and one cannot accept any estimate of the prevalence of the disease in this race. It is in the increasing mortality over the last few decades and in the



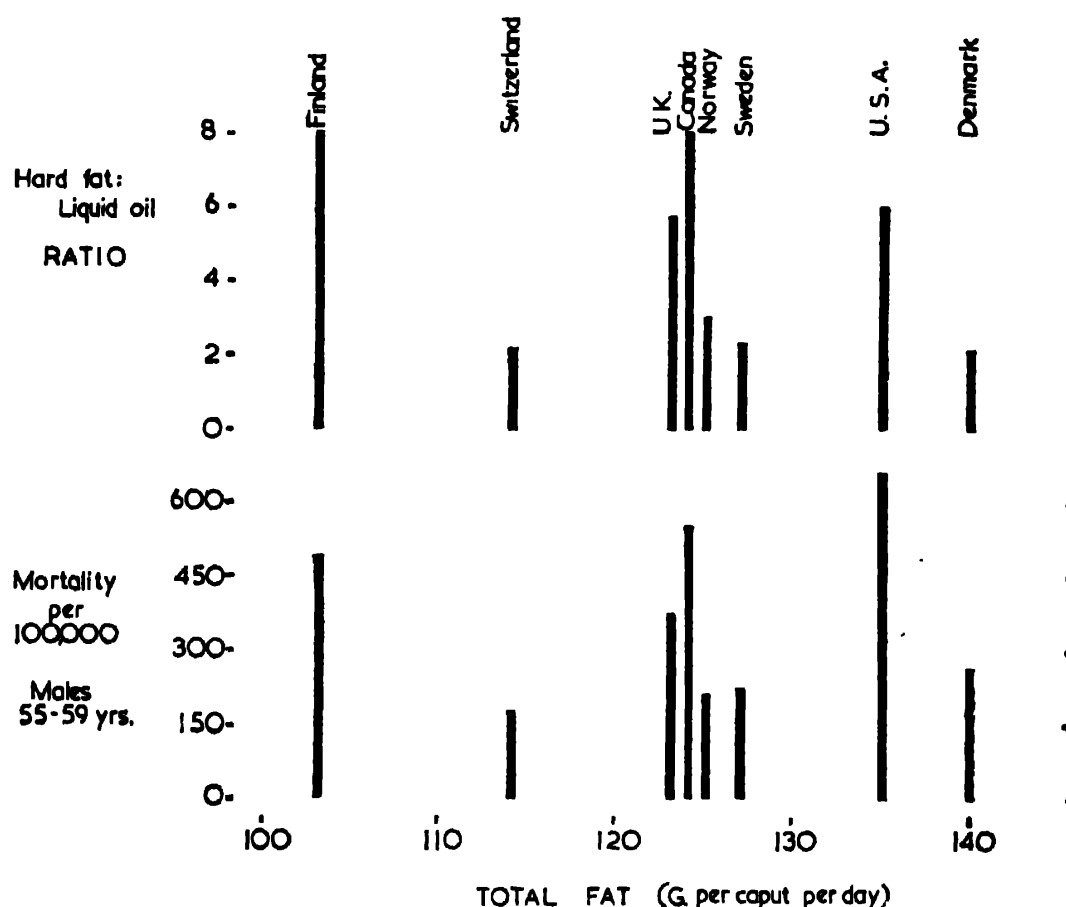
Based on Bronte-Stewart (1958).

FIG. 4. With minor variations, these differences are similar at all age ranges, with Scotland and Finland at the uppermost extreme and France and Italy at the lowermost. The mortality figures are somewhat higher in each case than as given with the key above. (Data from World Health Organization, 1956).

comparison between the mortalities in the European countries that qualitative rather than quantitative differences in the dietary fat intake explain better the reported differences in mortality from the disease.

With the increasing acceptance of hydrogenated products by the housewife, the increasing use of processed germ-free breakfast cereals and highly refined flours, there has been a considerable qualitative change in the dietary fat intake over the last few years.⁴⁶ There has been too, a decreased demand for fish. Current develop-

ments in animal husbandry concerned with greater productivity may have induced other changes. It is claimed, for example, that the composition of animal fat is dependent upon what the animal or bird is fed.^{4, 54} There has been then, a rise in the consumption of fats containing predominantly saturated fatty acids at the expense of the polyunsaturated fatty acids.



Based on Bronte-Stewart (1958).

FIG. 5. Qualitative differences in the available fat for consumption correlate with the different European death-rates from ischaemic heart disease better than quantitative differences. Canada and U.S.A. are included in this figure for comparison.

With the exception of Finland, Scandinavian death rates are between one-third and one-half of those in the United States and Britain yet the total fat intakes are roughly the same (see Fig. 4). The types of fatty foods contributing to these similar fat intakes are quite different. From the food balance sheets of the Food and Agricultural Organization,²⁴ one may obtain an approximate estimate of this by computing the ratio of consumption of hard fats, i.e. all animal and hard vegetable fats to liquid oil consumption which

includes vegetable oils and fat content of fish, cereals, nuts and so on. If one plots against the total fat intake of each country, firstly the corresponding death rate and secondly this ratio, a remarkable parallelism emerges (see Fig. 5). This parallelism is achieved only by the use of all three parameters. Danes with a high fat intake and low mortality, consume a great deal more fat in the form of liquid oils whereas the high mortality of the Finns was associated with the fact that most of the relatively low total fat intake was composed of hard fats. One could assume then that the liquid oils are protective at high fat intakes, bearing then, some relationship to the requirement of essential fatty acids in the experimental animal.

The interpretation of these data as being due to a deficiency of EFA relative to the total fat intake is influenced by the widespread metabolic effects relating to EFA deficiency in the animal. The similarity of behaviour on serum cholesterol levels of marine oils and vegetable (seed) oils has led to the argument that it is the number of double bonds and not the essential fatty acid content that is responsible for the effects shown. Neither cod liver oil¹⁷ nor a fish body oil such as menhaden oil¹ are able to cure all the features of EFA deficiency in the rat. It does not follow, however, that only these fatty acids are essential to man. Nevertheless these definite differences in metabolic behaviour in man of the various dietary fats, together with the close correlation that exists between the epidemiological features of ischaemic heart disease and the qualitative rather than the quantitative nature of the dietary fat intake, has provided the lead for more intensive study. With this comes great hope that the environmental factor responsible for the increasing mortality may be determined and eventually brought under control.

Application to Theories on the Pathogenesis of Ischaemic Heart Disease. The possible mechanisms whereby an excessive or imbalanced dietary fat intake could lead to ischaemic heart disease depends upon an assumption that atherosclerosis forms the underlying basis of the occlusive disease of the coronary arteries. The two major constituents of the atheromatous plaque are fibrin and fat. It is not unnatural therefore, that most theories on its pathogenesis revolve around fibrin or fat, though considerable controversy exists as to which component is primary and which is secondary. The fat in the atheromatous plaque bears a superficial resemblance to that in the plasma, with a high cholesterol and cholesterol ester content.³⁸ The arterial wall is capable of synthesizing cholesterol¹⁸ but the finding that the plaque contains carotenoid pigment,⁷ which cannot be synthesized and migrates electrophoretically with the beta

lipoprotein fraction of the plasma, would suggest that at least some of the fat is deposited there.

*The filtration theory*⁵¹ implies that the centrifugal forces of the circulation drives fat into contact with the intima and that lipid deposition accumulates over the years, but is accelerated or intensified in the presence of abnormal blood lipids especially if the intraluminal filtration pressure is high and if the permeability of the intima is increased. This theory offers an explanation for the characteristic focal distribution of atherosclerosis at sites of turbulence or velocity change, the increased severity of atherosclerosis in the presence of a raised blood pressure and in known lipid metabolic disorders as diabetes mellitus, myxoedema, essential xanthomatosis and renal disease. The maintenance of abnormally high serum cholesterol levels by the habitual consumption of excessive amounts of animal and other hard fats would explain then, the increased susceptibility to the disease in the more prosperous Western industrialized countries.

The relationship of coronary atherosclerosis to ischaemic heart disease is by no means clear. It is well known that severe coronary atherosclerosis may exist at autopsy without any deleterious effects on health. Conversely in a considerable proportion of cases with undoubted myocardial infarction, no subtending occlusion could be found despite careful dissection.^{8, 65} Morris⁴⁸ in drawing attention to the increasing mortality from ischaemic heart disease, presented evidence that the severity of atherosclerosis has remained unchanged or even declined over the last few decades. This has revived a great deal of interest in thrombotic and other mechanisms that could interfere with small vessel flow.

The thrombogenic theory of atherosclerosis implies that the initial lesion is a deposition of fibrin on the intima which becomes organized and endothelialized.²¹ Atherosclerosis then, could represent a failure of the delicate balance of fibrin deposition and fibrin removal.³ Several studies soon claimed that both blood coagulation and fibrinolysis were affected adversely following the feeding of high fat meals. Lipaemic blood was associated with a shortening of the whole blood siliconized clotting time and prolongation of lysis time; the latter particularly after the feeding of animal or hard fats. Greig²⁶ believed that the greater the intake of animal fat, the more persistent would be the inhibition of fibrinolysis and the greater the prevalence of severe atherosclerosis and thrombotic episodes. Further studies did not confirm these findings and while there is no doubt that the "stypven" plasma clotting time is shortened following

the feeding of fat, there is a considerable inconsistency in the other tests studied and this inconsistency is probably due to the insufficiently refined techniques used.⁴⁵ At the same time it should be emphasized that we are as yet unaware of the relation these *in vitro* clotting tests bear to the overall problem of thrombosis *in vivo*, but it is of interest in this regard to note the abrupt fall in thrombo-embolic complications during the severe rationing period of the war in Norway.⁵⁸

Other effects noted during the lipæmic phase that may have a bearing on the pathogenesis of atherosclerosis and ischæmic heart disease concern red cell flow in small vessels. Swank and his colleagues^{59, 60} have shown with both *in vivo* and *in vitro* studies that late in the lipæmic phase the red cells become aggregated with slowing of flow in small vessels. This, together with obstruction due to intravascular fat globules resulting in widespread tissue ischæmia probably accounts for the lethal effects of a circulatory overload of fat in certain animals. In man, exacerbations of anginal pain with electro- and ballisto-cardiographic changes have been reported between 3–5 hours after a fatty meal³⁶ but these findings remained unconfirmed despite the many fat tolerance tests performed since.

Patients with ischæmic heart disease exhibit a more intense and more prolonged lipæmia than controls after a standard fat meal.^{5, 13} This too, has been claimed as a possible mechanism in that prolongation of the lipæmic phase could allow prolonged contact of lipid with the intima.⁴⁷ Certain evidence suggests that the antecedent nature of the diet with regard to fat quantity and fat quality may determine this lipæmic response.^{13, 52}

There are therefore a great many theories that link quantitative and qualitative changes in the dietary fat intake with the development of atherosclerosis and ischæmic heart disease. The dietary fat hypothesis depends on the strength of the links in the relationship between diet, serum lipids, atherosclerosis and ischæmic heart disease. Controlled feeding experiments give undeniable proof that diet influences serum lipid levels, but there is no proof that the change shown has any bearing on the development of ischæmic heart disease. The link between diet and the development of ischæmic heart disease is founded firstly on the production of atherosclerosis in the animal and on epidemiological evidence in man. The nature of the lesion produced in the animal makes extrapolation from animal to man unwise whereas in the interpretation of epidemiological data, one must be aware of the great many variables operating, some of which are not as yet subject to measurement. Neither in the underlying

pathology of ischaemic heart disease nor in the pathogenesis of atherosclerosis is there unanimity, and in studies on homogeneous groups there is considerable overlap in the serum lipid abnormalities reported in ischaemic heart disease between patients and controls, particularly at the very age at which the disease is most common.¹⁰

On this background one has to acknowledge that the hypothesis is applied to a disease most difficult to measure in its prevalence and to predict in its mode of progression. In part these difficulties arise from the fact that as yet it is not easy to study the disease in its development. It is a disease of man's later years and his life cycle is such that recourse has to be made to the study of groups, to the study of the disease at different ages, and to the study of the disease at different times and different places. In such instances it is true that differences in dietary fat intakes are seen but other variables have been at play. For ischaemic heart disease we have yet to discover the ideal circumstances, to seek some naturally-occurring groups where Nature has performed a good experiment; an experiment in which one variable alone has been altered, the others remaining constant.

Dietary Therapeutic Trials. To date there are no controlled clinical trials on the effect of diet on the outcome of ischaemic heart disease. In 1936⁴³ it was claimed that severe dietary restriction almost halved the mortality in the early period following a myocardial infarction. Unfortunately in this study the comparisons were made with the mortality experience in different years. There are two long-term trials on the effect of dietary fat restriction but neither has made allowance for the quality of the fat in the diet. Morrison⁴⁹ studied 100 cases of cardiac infarction for eight years. Half the cases were induced to consume only 20–25 g. of fat daily while the remainder continued to eat between 80 and 160 g. of fat a day. In the dietary fat-restricted group, 28 of the 50 were still alive and only 9 of the 22 deaths were attributed to cardiovascular causes. In the unrestricted group only 12 were still alive and 22 of the 38 deaths were from cardiovascular causes. Lyon and others³⁹ studied 280 patients with myocardial infarction for four years. A maximum of 50 g. of fat a day was allowed to 165 patients, amongst whom there were 15 recurrent infarctions and four deaths. In 115 patients who continued on an unrestricted diet, there were 31 recurrent infarctions with 13 deaths. Neither can claim to fall into the category of a controlled clinical trial however.

Possibly the reason why more reports are not available is due to the difficulty with which one variable only is altered in a dietary trial. Prospective studies undertaken at present³² are imperative but are

likewise difficult, as the age at which the stage is set is unknown, and factors other than diet undoubtedly enter into the causation of the fully evolved picture. By the age of 20, the serum lipid levels are different, dependent on race and economic background¹⁰ and a severe degree of coronary atherosclerosis was already present in the young U.S. soldiers autopsied in Korea.²²

The implications of the dietary fat hypothesis are that trends in modern diets of the western industrialized nations over the past few decades have allowed an increase in the consumption of saturated fatty acids at the expense of or without a sufficiently concomitant increase of the polyunsaturated fatty acids. The dietary fat hypothesis implies that this leads to a disordered lipid metabolism which over the years leads to atherosclerosis and possibly is one of the major contributing factors to the final picture, ischæmic heart disease. These implications are wide, affecting developments in animal husbandry, food processing and the health education of our youth. For these reasons it is perhaps desirable to demand a great deal more factual information before widespread application is practised. Nevertheless if one accepts that an environmental factor is at the background of the alarming increase in mortality from ischæmic heart disease, of all those that constitute our present-day mode of life, no other at present known, can be so closely related to pathological, metabolic and epidemiological features of the disease as the nature of the dietary fat intake.

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CHAPTER 20

ABNORMALITIES OF FLUID AND ELECTROLYTE METABOLISM IN MALNUTRITION IN ADULTS

by

L. EALES

THAT abnormalities of fluid and electrolyte metabolism may be encountered as a result of experimental starvation and during chronic undernutrition and famine is well established. While these abnormalities may be modified by variation in intake of both fluid and electrolyte, the effects of complicating or concomitant disease must always receive due consideration.

With the current interest in water and electrolyte metabolism several treatises covering this field have appeared but the effects of malnutrition receive scant attention in such excellent books as those of Black⁵ and Elkinton and Danowski.¹⁵

With the development of methods for investigating body volume and composition, our knowledge has been materially advanced. The introduction of isotope dilution studies has stimulated extensive investigations into body composition in many clinical conditions. The various methods used have been ably summarized by Elkinton and Danowski¹⁵ and the difficulties of interpretation are discussed. A technique of more or less simultaneous investigation of several aspects of body composition, and volume has been developed by Moore *et al.*³¹ and can be completed in 36 hours. Although subject to error on account of the repeated sampling and the removal of as much as 200 ml. of blood it has provided important information. It is possible to measure the blood volume, total body water and extracellular fluid volume, intracellular K, extracellular Na and Cl. In Table 1 the results in a 60-year-old male (70 kg.) and a 60-year-old female (60 kg.) are taken from Moore *et al.*³¹

The results are most simply expressed as a percentage of observed body weight or as mEq./kg., but if necessary the pre-illness (or "normal") weight may be used. It is obvious that such measurements will vary according to age and sex. The chief advantage of weight as a reference is the ease and accuracy of measurement. Body weight is only really satisfactory when lean tissue mass is the point of reference.

TABLE I

<i>Measurement</i>	<i>Male (70 kg.)</i>		<i>Female (60 kg.)</i>		<i>Method</i>
	<i>Absolute value</i>	<i>Relative value</i>	<i>Absolute value</i>	<i>Relative value</i>	
Total body water . . .	39.8 L.	56.8%	29.1 L.	48.5%	Deuterium
Extracellular water . . .	16.4 L.	23.4%	14.2 L.	23.7%	Radiobromide
Plasma volume . . .	3,150 ml.	4.5%	2,700 ml.	4.5%	Evans blue
Red blood cell volume . . .	2,100 ml.	3.0%	1,500 ml.	2.5%	Radiochromide
Blood volume . . .	5,250 ml.	7.5%	4,200 ml.	7.0%	Evans blue + radiochromate
Total exchangeable sodium	2,870 mEq.	41 mEq./kg.	2,460 mEq.	41 mEq./kg.	Radiosodium
Total exchangeable potassium . . .	3,300 mEq.	47 mEq./kg.	2,400 mEq.	40 mEq./kg.	Radio-potassium
Total exchangeable chloride . . .	2,030 mEq.	29 mEq./kg.	1,740 mEq.	29 mEq./kg.	"Bromide to chloride specific activity"

Adapted from Moore *et al.*³¹

From these values others may be derived.³¹ Many of these while subject to additive errors are of interest. Total body solids is obtained by subtracting total body water from body weight and is the most reliable derivation. Total body fat can be calculated but is unreliable in the presence of oedema. The solids less fat give lean tissue mass while total body water minus extracellular water gives the intracellular water. "Residual Na" represents the difference between Na_e^* and the product of $\text{ECF}\dagger$ volume and serum Na concentration.

Starvation States and the Syndrome of Depletion

Using these techniques, Moore *et al.*³¹ have studied what they have termed the starvation states and the "syndrome of depletion". Chronic energy deficits occur in chronic infection, malignancy, repeated trauma or prolonged acute illness passing into a chronic phase. Some degree of cachexia is present in all of these patients. The findings in a heterogeneous group of patients with the above conditions were similar:

A normal or near normal blood volume; a high plasma volume but low red cell volume. Normal total body water; markedly increased ECF (in relation to actual body weight); a high total Na and Cl; reversal of Na_e^* and K_e^* ratio; low intracellular water and low K_e^* . Thus the outstanding volume abnormality was the increased ECF but when this is related to the patients' "normal" body weight, $\text{ECW}\dagger$ is normal while $\text{ICW}\dagger$ is reduced. The enveloping skin and subcutaneous tissue is too large relative to the body's working tissue. This condition is thus very similar to the findings in the early phases of starvation oedema.

In such patients a low serum Na and a slightly raised serum K concentration is frequently encountered and may be regarded as the pointer to the altered body composition. This asymptomatic hyponatraemia¹⁴ is to be distinguished from that of true Na depletion and that of water excess—so-called dilution hyponatraemia. The hyponatraemia of the starvation-depletion state may reflect a failure of the "Sodium pump". The cell requires energy to extrude Na. With the lack of energy this mechanism fails, and hence Na concentration rises in the cell. Water is not excreted properly and with the new water derived from tissue oxidation the whole body becomes hypotonic. While the administration of potassium²⁸ will raise the serum sodium in a variety of hyponatraemic conditions, Moore³¹

* Na_e and K_e = Exchangeable sodium and potassium.

† ECF = Extracellular fluid, E. and ICW = Extra and Intra-cellular Water.

believes the fundamental need is for energy and claims that correcting the calorie deficit will result in restoration of body composition to normal accompanied by a rise in serum sodium concentration.

Body Composition in Starvation Œdema

The most striking abnormality is undoubtedly œdema but this is by no means constantly present in malnourished individuals and in those with hunger œdema there is a prolonged period of inadequate diet prior to the appearance of œdema. During this pre-œdematous phase characteristic changes occur in the composition of the body and the distribution of the body fluids.

Plasma is the most readily sampled moiety of the body fluids but variations in electrolyte concentrations are uncommon in cases of undernutrition. Keys *et al.*²⁷ reported no consistent changes while Srikantia *et al.*³⁸ noted low "normal" levels of sodium, subnormal chloride levels and "high normal" K levels. Elkinton and Huth¹⁶ in reviewing the serum electrolyte changes in experimental and clinical undernutrition state that hypokalaemia appears to be the only frequently encountered abnormality, and reported that hypochloræmic alkalosis, hypokalaemia and hyponatraemia occur in a proportion of patients with anorexia nervosa but the situation is complicated by the occurrence of vomiting. While such investigations alone may provide little help in assessing actual changes in body composition, a determination such as serum K concentration when properly interpreted is a good guide to the body's requirements.³⁴

In contradistinction to the obvious reduction in fat and the tissue wasting there is an increase in the ECF space relative to total body water.

In prolonged semi-starvation as in the Minnesota experiment²⁷ both plasma volume and thiocyanate space remained on an absolute basis almost at pre-starvation level. Therefore there is an increase in the amount of fluid in the extracellular space per unit of body weight. Beattie *et al.*³ in their studies on Dutch and German adult males found that the thiocyanate space amounted to 34.2 per cent of actual weight but the absolute value was only slightly larger than the normal value for individuals of similar age and weight. The relative thiocyanate space remained above normal despite the disappearance of œdema. They also observed that with the fall in body weight in undernutrition the percentage of body weight occupied by the ECF phase necessarily increases and when this increase amounts to approximately 10 per cent (± 5 litres) œdema is likely to appear. In good agreement is Keys'²⁷ observation that after 24 weeks of starva-

tion the average excess of ECF was 10.48 per cent, but not all of his subjects exhibited oedema.

While this increase in ECF volume is generally accepted, expansion of the intracellular fluid volume has been the subject of differing views. Keys *et al.*²⁷ felt that the probability is that there is some intracellular oedema in starvation. Gopalan *et al.*²¹ and Holmes *et al.*²⁴ have concluded that cellular overhydration existed in their protein deficient subjects, but Widdowson and McCance *et al.*⁴³ studies on their undernourished subjects at Wuppertal (urea space) did not appear to support cellular overhydration.

Nutritional Oedema

In many parts of the world oedema in adults resulting from under-nutrition has been intensively investigated and described under the names "famine oedema", "starvation oedema", "hunger oedema" and "war oedema". The subject has been extensively reviewed by Keys²⁷ and McCance.³⁰ This type of oedema commonly occurs in previously healthy and well-nourished people who have been subjected to relatively acute and severe food deprivation. In some areas acute undernutrition may be superimposed on a long history of chronic undernutrition or chronic malnutrition. In other patients such as the destitute beggars of Gopalan²¹ who were in an advanced state of chronic starvation, the diets had been grossly inadequate for several years. Thus in malnourished or undernourished patients a multiplicity of factors is involved. These include: not only caloric insufficiency due to diminished carbohydrate and fat intake, but also frank protein deficiency. In addition, vitamin deficiency either relative or absolute, is to be considered. Thiamine is particularly important in this connection.

Study of nutritional oedema¹³ in the Non-White adult population of Cape Town has revealed the complexity of the processes involved and has prompted the use of the general designation "nutritional oedema" as an abbreviation for the somewhat cumbersome phrase "oedematous syndromes associated with chronic malnutrition". The term "nutritional oedema" is used in the widest sense and includes all forms of oedema wholly or mainly resulting from undernutrition or malnutrition. Included under this term is not only starvation oedema but even beri-beri and other conditions in which cardiac failure contributes to the oedema, because the role of cardiac failure is often not separable from that of other mechanisms in the production of oedema.

For an account of the dietary habits and *modus vivendi* of the Bantu, see p. 4. In these people the early symptoms of ill-health tend to be ignored until finally œdema or other disabling symptoms necessitates their admission to the hospital. Representative examples of the types of nutritional œdema were reported (Eales *et al.*¹³) as follows:

- I. Nutritional œdema responding to bed rest only.
- II. Nutritional œdema responding to bed rest only (temporary abnormal electrocardiogram).
- III. Nutritional œdema of "Beri-beri type".
- IV. Nutritional œdema—intractable congestive cardiac failure.

Similar cases occur in Cape coloured patients, but only rarely are such cases seen in the white race where most nutritional deficiency is associated with alcoholism. Apart from these cases of œdema in the adult, kwashiorkor is commonly seen in children. In addition, the conditioning effects of defective gastrointestinal absorption and metabolism must not be forgotten in individuals existing on marginal diets.

A working classification based on our experience at Groote Schuur Hospital follows:

1. The œdema of caloric undernutrition and protein deficiency.
 - (a) Hypoalbuminæmic œdema (i) Adult; (ii) Child—kwashiorkor.
 - (b) Œdema with normal or near normal serum albumin. (Isohydric famine œdema.³⁶)
2. The œdema of cardiovascular disorder.
 - (a) Acute beri-beri.
 - (b) Cardiomyopathy of unknown origin. (? Nutritional heart disease.)
 - (1) Acute reversible heart failure of unknown origin.
 - (2) Chronic intractable heart failure.
3. The œdema of hepatic disorder. Bantu cirrhosis.

Œdema of Caloric Undernutrition and Protein Deficiency. It is difficult to separate the effects of pure calorie deficiency from calorie plus protein deficiency. Although it has been customary to consider hypoalbuminæmic œdema separately, it is clear that there is much overlapping in the adult. In the child with kwashiorkor œdema and hypoalbuminæmia generally go hand in hand. While this disorder is held to be largely the result of protein deficiency the diets are also

defective in fat and vitamins. Furthermore the modifying influences of variations in the sodium and potassium intake have to be considered as has the influence of complicating infection.

For many centuries œdema has been accepted as a common manifestation of malnutrition in the adult. The clinical characteristics of hunger œdema have been succinctly described by McCance.³⁰

1. The appearance of œdema is preceded by a considerable weight loss.
2. It occurs characteristically in men over the age of 40.
3. Men are more commonly affected than women.
4. It is always accompanied by polyuria, especially at night. This polyuria may antedate the œdema by several months but many who have nocturnal polyuria never develop œdema.
5. The œdema first appears in the evenings in the dependent parts, or in the mornings in the face. It is very much affected by posture and often disappears with bed rest.
6. Exercise makes the œdema worse.
7. The œdema tends to recur. It may persist for months or even years after all other signs of undernutrition have vanished.
8. There is little evidence of kidney involvement. The kidneys are able to produce concentrated urine under the appropriate conditions.

In hunger œdema the history is not of total starvation but of prolonged undernutrition, the diet being predominantly a carbohydrate one, as in the subjects studied by Sinclair,³⁵ Beattie *et al.*,² and by McCance³⁰ in Europe or in the Prisoners of War investigated by Smith *et al.*³⁶ in the Far East. Although œdema tends to develop as a result of prolonged feeding on a diet low in protein but by no means totally deficient in calories, Smith *et al.*³⁶ thought that protein deficiency was unlikely since in Hong Kong protein intake ranged between 40–60 g. daily and in Singapore from 30–90 g. The protein, however, was almost entirely vegetable in origin. The detailed studies during human experimental starvation have been most illuminating. The Minnesota subjects subsisted on a diet deficient in calories and containing 49 g. protein daily.

Although many of these subjects developed œdema, the plasma protein concentrations were reduced by only 10 per cent from 6.85 g. per cent to 6.10 g. per cent. This observation and Sinclair's³⁵ findings that the presence or absence of œdema was independent of protein and albumin levels and the lack of correlation between grade of œdema and serum albumin level noted by Kekwick³⁶ in 16 of the

Wuppertal subjects, casts considerable doubt on the exact part played by hypoalbuminaemia in the genesis of the oedema.

Between the wars hypoalbuminaemia was commonly held to be the explanation of famine oedema. That it is a factor in some cases cannot be denied but it is clear, however, that many cases of famine oedema cannot be explained entirely on the basis of Starling's hypothesis.

There is little evidence of renal dysfunction, but there is little doubt that the pituitary and the adrenal play an important role in the genesis of the oedema. Whereas the role of antidiuretic hormone (ADH) in the regulation of the "effective" osmotic pressure of the extracellular fluid and thus in the homeostasis of the intracellular fluid is well established, its role in oedema is less certain. While it is true that substances with antidiuretic activity have been found in the urine of patients with oedema, there is no proof that these are in fact true ADH. The low serum sodium seen in some oedematous patients may be interpreted as a result of ADH action and a diuretic response following inhibition of ADH by ethanol ingestion in such patients suggests increased ADH activity to have been operative.

The finding of a raised aldosterone excretion in generalized oedema due to cardiac, renal, and hepatic causes is well established. It is generally agreed that the control of the excretion of sodium is related to aldosterone action which thus directly influences the body sodium and the ECF volume. Reports of measurements of aldosterone output in nutritional oedema are scanty. Elevated values have been found in children with kwashiorkor.^{6, 39} The possibilities of the defective hepatic metabolism of cortisol and oestrogens have also to be considered.

Among the Bantu patients (oedema with normal heart and ECG) oedema is noted to be subject to the characteristic effect of posture, and the prompt disappearance on recumbency while still on the deficient diet leads one to question the unwarranted assumptions that have been made on the effects of therapy in such patients particularly in respect of "response to thiamine".

The Oedema of Cardiovascular Disorder. Myocardial failure of uncertain aetiology is frequently seen in the less developed regions of the world, but does occur although relatively rarely in the highly developed zones where the most common cause of isolated myocardial disease is coronary disease. The aetiology is bathed in obscurity and our ignorance is reflected in the confusing array of terms—cardiopathy, myocardopathy, myocardosis and even myocarditis, etc.

We must, however, emphasize that these cases of apparently causeless heart failure do occur both in the tropical and the non-tropical zones in a people who have from infancy been subjected to chronic undernutrition with or without phases of acute deprivation. Furthermore the occurrence of similar syndromes in Europeans and North Americans who are addicted to alcohol again suggests that faulty nutrition is a factor to be considered. A syndrome such as oriental beri-beri is easily recognized, but there has been a tendency in recent years especially in the United States of America to include under the heading of beri-beri cases of cardiac failure particularly in alcoholics in which the picture is far removed from the oriental type and are better included under the title of cardiomyopathy of uncertain origin or alcoholic myocardopathy.

Acute Beri-beri. The picture of oriental beri-beri is well known. It is a predominantly right-sided heart failure with venous congestion but at the same time evidence of a hyperkinetic circulation, warm hands, bounding pulse, and pistol shot sounds over the larger arteries. Syncope frequently complicates the course. It occurred in patients subsisting on rice and was associated with signs of neurotic involvement. The electrocardiogram may show non-specific changes. Reversal to normal follows administration of thiamine. Weiss and Wilkins⁴² drew attention to the occurrence of a similar picture encountered mainly in alcoholics but stated that left ventricular failure with dyspnoea and pulmonary congestion was just as frequently observed. Following this Blankenhorn⁷ listed certain criteria for the diagnosis of beri-beri, and in many subsequent uncritical reports cases of obscure congestive failure have been attributed to beri-beri—even in the face of failure to respond to thiamine therapy!

Beri-beri is frequently seen in South Africa.^{13, 19, 33, 40} Suzman⁴⁰ was the first to describe such cases. It is probable that some of Gillanders'²⁰ cases of nutritional heart failure were cases of beri-beri. The clinical features as seen in Cape Town in the three races is similar.

Excessive ingestion of alcohol coupled with an inadequate diet is almost invariably present. Anorexia, epigastric discomfort, and early morning vomiting is frequent. Peripheral neuropathy involving the legs with diminished or absent tendon reflexes, marked increase of deep pressure pain in the calves and hyperæsthesia of the soles of the feet is usually present. Occasionally encephalopathy with confusion, and nystagmus and brain-stem involvement is seen. Heart failure is present without evidence of valvular or ischæmic heart disease.

Not infrequently there is hypertension, but this is usually transient. Despite the elevated venous pressure, evidence of a hyperkinetic circulation (warm hands, a collapsing pulse, and a shortened circulation time) is noted at some stage of the illness in the majority of cases. Evidence of left ventricular failure is sometimes seen. Abrupt transition from hyperkinetic failure to a profound hypokinetic state has been observed on more than one occasion. X-ray of the heart shows generalized cardiac enlargement with rapid reversal to normal on treatment with thiamine. Complete recovery is the rule. The ECG is of help in diagnosis. Following thiamine therapy, Suzman noted apparent deterioration in the ECG picture during clinical improvement—a finding also described by Weiss and Wilkins.⁴² The most extensive investigation in the ECG picture of beri-beri is that of Gant and Schrire¹⁹ who stress the special value of serial electrocardiography. A normal ECG at the height of failure is very suggestive of beri-beri. Serial changes are important too. Despite recurrent episodes of failure, return to normal is noted. In a few cases, beri-beri heart disease co-exists with other forms of heart disease. The differential diagnosis has usually to be made from pericarditis and myocardial failure of unknown origin, though hypertension occasionally gives rise to difficulty.

Unexplained variations in the brachial blood pressure have commonly been observed in the Groote Schuur Hospital cases and have been reported by other workers.⁴¹ The hypertension present on admission in a case of beri-beri often suggests the possibility that idiopathic hypertension, rather than beri-beri, is the cause of the congestive failure. The evidence for cardiovascular hypertrophy is, however, usually absent in the larger palpable arteries and in the retina, and the hypertension usually subsides, sometimes very rapidly, under treatment.

There has been much speculation about oedema resulting from thiamine deficiency in the absence of clinically recognizable heart failure.³⁶ Grusin's²² cases of nutritional oedema with a normal heart size may be examples of this condition. Undoubtedly many cases of beri-beri are suffering in addition from deficiency of nutrients other than thiamine; in other words they are mixed cases. Frequently the serum albumin concentration is low. It is preferable to keep an open mind on the question as to whether thiamine deficiency can cause oedema in the absence of cardiac failure, and on the question as to whether the oedema of beri-beri is always wholly due to cardiac failure.

Although alterations in serum electrolyte values occasionally are

seen they were not consistent. While there may be accumulation of lactate and pyruvate in the tissues there is no reason to suspect in beri-beri that the abnormalities of body fluids and electrolytes differ materially from those in congestive failure due to other causes in which there is a marked increase in total body sodium. Iseri *et al.*²⁵ have studied 3 alcoholic patients diagnosed as beri-beri with high output congestive failure. This was established clinically and by cardiac catheterization. Metabolic balances of sodium, potassium, chloride and water were studied during recovery. Treatment during this period included bed rest, and a low-sodium, vitamin-rich diet. There was a pronounced cellular uptake of potassium in all 3 patients and a significant negative intracellular water balance and the trends were similar to those seen in other cases of low-output congestive heart failure. The findings in congestive heart failure have been ably reviewed by Friedberg.¹⁸ The disproportionately high retention of sodium relative to water throughout the body while the concentration of sodium in the ECF is normal or low, may be taken to indicate that sodium penetrates the cells or some other reservoir such as bone, cartilage, or connective tissue. Despite their limitations, investigation by isotope dilution techniques and balance studies during recovery from heart failure and tissue analysis have generally indicated that intracellular sodium is increased. Similarly measurements of K_e , balance studies, and muscle biopsy have indicated a diminution in total body potassium and since total ECF K is increased, the intracellular stores must be reduced. Effective treatment reverses these findings. The potassium depletion is in part due to the general cellular catabolism since negative nitrogen and phosphorus balances co-exist with a negative potassium balance.

While prompt response to thiamine is looked on as essential for the diagnosis of beri-beri, the effects of bed rest alone must be taken into account. Bed rest may initiate diuresis not only in beri-beri as in case 1 of Iseri *et al.*²⁵ but in many cases of oedema due to other causes including the congestive failure of cardiopathy of unknown origin. Fig. 1 illustrates a prompt response to thiamine during a second attack of beri-beri.

To obviate the effects of recumbency itself, and to counteract the possibility that bed rest might lessen the tissue demands for thiamine, this patient was not confined to bed. In addition the effects of a low-sodium diet have to be considered. The sodium intake was maintained at 100 mEq per day. As can be seen, the diuresis commenced on the second day.

While the response is usually prompt, the possibility of complicat-

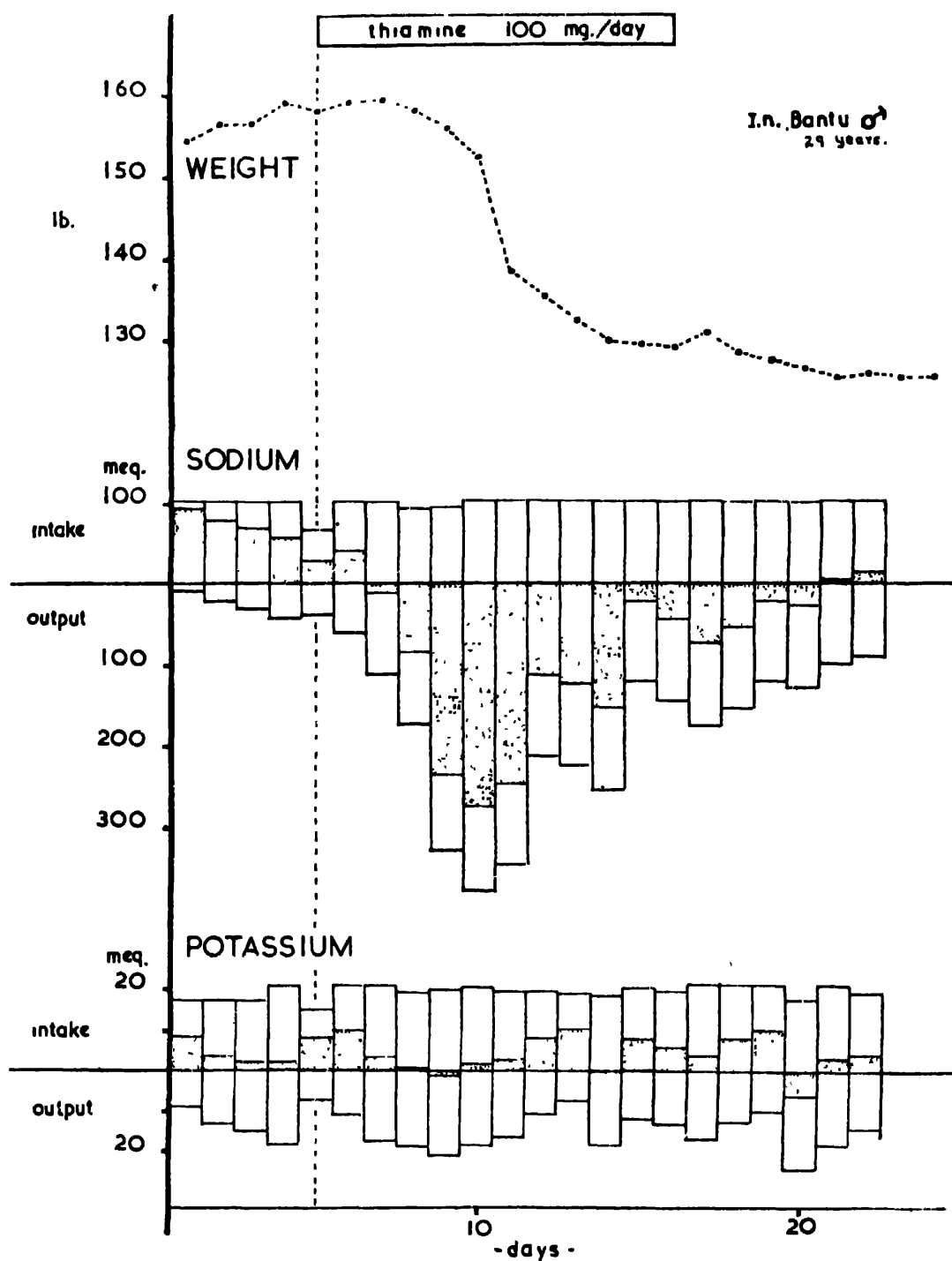


FIG. 1. The Na and K balance during a second attack of beriberi in a Bantu male. The stippled areas represent the daily balances. Patient remained ambulant.

ing factors must be borne in mind. In beri-beri, serum K concentrations are usually within normal limits or slightly reduced. The effects of anorexia and vomiting are to be considered. Rare instances of hyperkalæmia are referable to oliguria and prerenal azotæmia.

Sufficient potassium must be available before thiamine can be effective. This is illustrated in the accompanying Fig. 2.

The patient, who drank excessively, had heart failure with marked venous congestion and a hyperkinetic circulation. There was marked peripheral neuropathy—despite a grossly enlarged heart the ECG was normal. To obviate the complicating effects of recumbency he was not confined to bed. As can be seen during the period on the basal thiamine-deficient diet and later while receiving thiamine, there was no response although the ECG became abnormal. Three days following the institution of potassium supplementation (80 mEq./day) diuresis commenced. *Pari passu* with the diuresis there was a rapid restoration to normal and he was discharged 28 days after admission with a normal heart and ECG.

Apart from the depletion of intracellular potassium accompanying congestive failure, the possible further deleterious effect of a low-potassium high-sodium intake in the Bantu is to be remembered and is considered further on p. 214.

Cardiomyopathy of Unknown Origin. Although rare cases of heart failure caused by fibrosis of the endocardium have been reported from time to time, it was brought into prominence by Bedford and Konstam⁴ in 1946 who described from the Middle East a group of African soldiers mainly from West Africa with obscure heart failure. In some of them at autopsy extensive subendocardial fibrosis of the ventricles with adherent organized thrombi were found. Reports from Uganda, Davies,¹¹ Williams, Davies and Ball⁴⁴ and Davies¹² indicated that endomyocardial fibrosis (EMF) was a common cause of heart failure in Africans. Both sexes and all ages are affected. No case in a European or Indian resident has been reported. They present as cases of heart failure with no distinguishing characteristics or with incompetence of the AV valves, or they may resemble cases of constrictive pericarditis. Peripheral emboli rarely occur. In addition O'Brien³² has described 25 cases of EMF from the Sudan.

Cardiopathy of unknown cause is frequently seen in the Bantu population of South Africa, but it appears to differ from the condition as seen in Central Africa. The cases described by Gillanders²⁰ and Higginson, Gillanders and Murray²³ as instances of nutritional heart disease rarely showed extensive endomyocardial fibrosis. A few of the cases of Becker *et al.*³ designated "Cardiovascular collagenosis with parietal endocardial thrombosis" had some resemblance to EMF, but Davies¹² declares this disorder to be distinct from EMF. Cardiopathy of unknown origin is also well known in Cape Town but EMF is rare. Acute reversible heart failure, recurrent episodes of

SD—COLOURED MALE—36 years.

CASE No 17

BANTU DIET

THIAMINE

KCl

FULL DIET

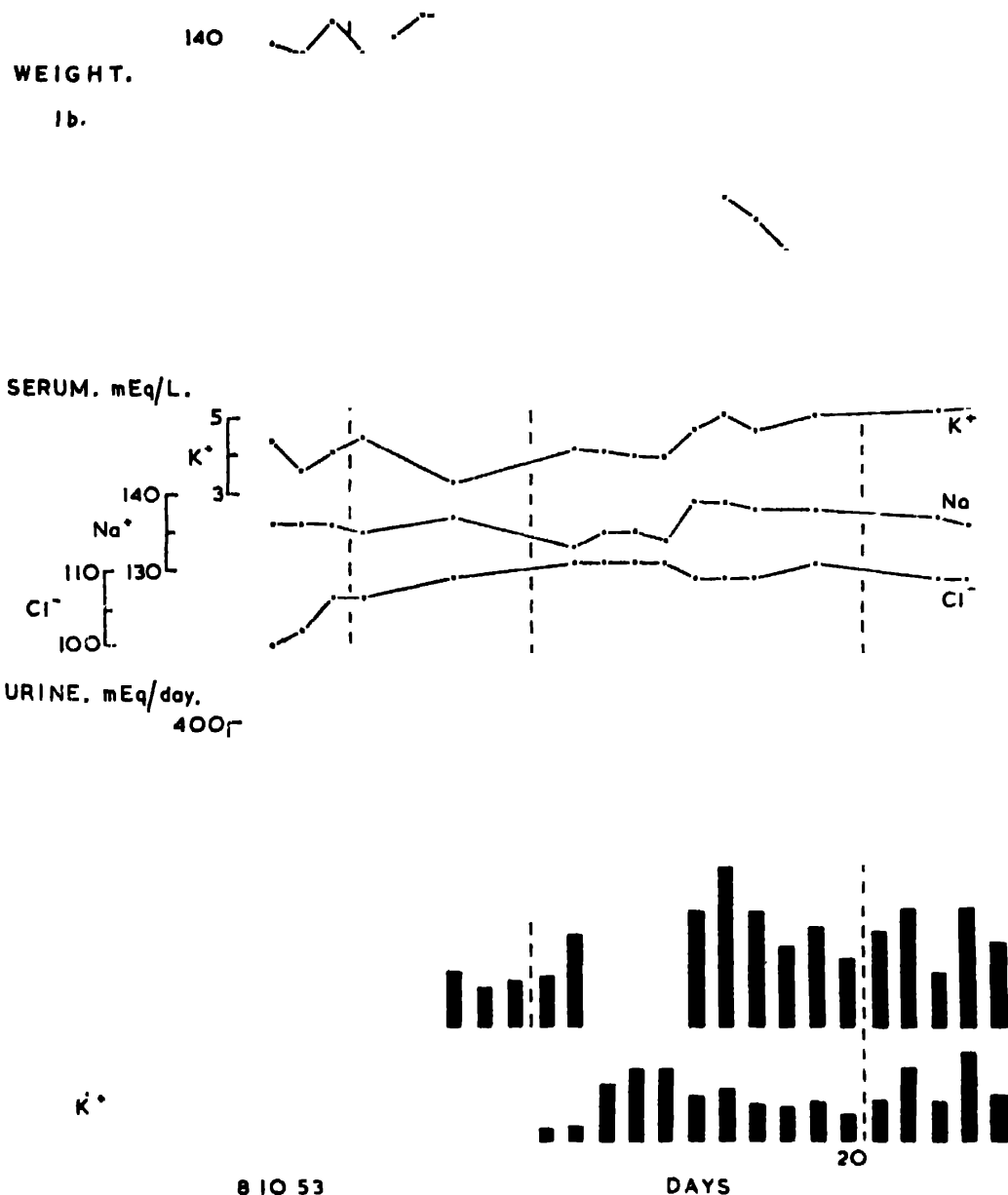


FIG. 2. Beriberi in an alcoholic Coloured male (aged 36 years). The "Bantu diet" consists largely of maize meal, a little white bread, treacle and tea and sugar without milk. (The Na content 100 mEq.; K content 15 mEq./day). There was a slight natruresis on day 4 of thiamine therapy, but he continued to gain weight and effective natruresis and diuresis started only 2 days after the inception of KCl therapy.

TABLE 2

<i>Race</i>	<i>Racial distribution of electrocardiograms</i>		<i>Racial distribution of 66 cases of beri-beri</i>		<i>Racial distribution of 62 cases of cardiopathy</i>	
	<i>No.</i>	<i>% of Total</i>	<i>No.</i>	<i>% of Total</i>	<i>No.</i>	<i>% of Total</i>
White .	7,537	57	22	33	8	13
Coloured .	4,795	37	25	38	20	32
Bantu .	820	6	19	29	34	55
Total .	13,152		66		62	

From Schrire, V.³³ (by courtesy of Editor, American Heart Journal)

congestive failure, and finally chronic irreversible heart failure are all seen. Over a 5-year period the electrocardiographic service of Groote Schuur Hospital³³ has obtained records of 62 cases of cardiopathy, of which 8 occurred in white, 20 in coloured and 34 in Bantu patients. Since only 6 per cent of the total electrocardiograms of the hospital came from Bantu patients, the great frequency of the condition in this group is obvious.

In the Bantu hypertensive heart disease, rheumatic heart disease, tuberculous pericarditis, cardiopathy (including beri-beri) and syphilitic heart disease are the common cardiac conditions, while ischaemic heart disease and pulmonary embolism are rare.

The clinical features resemble the cases described by Gillanders.²⁰ Undoubtedly some of these cases such as case 2 of our report¹⁵ who presented with oedema but with a normal heart size and an abnormal ECG might have been regarded as cases of beri-beri. The oedema, however, resolved while on a thiamine-deficient diet and without thiamine therapy. The ECG reverted to normal. That forms of acute reversible heart failure (not due to thiamine deficiency) occur is probable. Some of Gillanders' cases are possible examples as are some of Grusin's.

Relapses are frequent but usually sooner or later a state of chronic intractable heart failure is reached. Such cases are afebrile and there is no eosinophilia. Apparent involvement of central nervous system may be slight and overt dermal stigmata of malnutrition are not pronounced. Gynæcomastia, testicular atrophy and cirrhosis of the liver may be present. The clinical features are those of severe congestive heart failure of low-output type with normal rhythm. Frequently systolic murmurs are audible and a triple rhythm is almost invariably present. Extreme enlargement of the heart with feeble marginal pulsation is characteristic. In advanced cases functional tricuspid incompetence is frequent. The blood pressure is often low and the pulse pressure reduced. The ECG shows abnormalities of the T waves over the ventricular surfaces and the rapid alterations seen in many cases of beri-beri are not observed. The differentiation of these huge adynamic hearts from cases of gross tuberculous pericardial effusion is often a matter of considerable difficulty only to be resolved by cardiac catheterization, or paracentesis, or indeed open thoracotomy—since paracentesis is not without danger in the presence of a grossly dilated heart. The pathological features are dilatation and hypertrophy. Fine foci of fibrous scarring may be encountered; endocardial fibrosis and mural thrombi with peripheral emboli may be noted. In these severe cases of congestive heart failure

the response to digitalis is frequently disappointing and œdema can with difficulty be improved by the use of mercurial diuretics. The benefits arising from prolonged bed rest need more emphasis. Burch and Walsh⁹ has reported remarkable improvement in cases of obscure heart failure.

As mentioned previously, similar cases are seen in white subjects but in most of these there is gross alcoholism. There are many reports of beri-beri in alcoholic subjects and in the face of failure to respond to thiamine therapy the diagnosis is open to considerable doubt. While this raises the possibility of irreversible changes following acute beri-beri—a possibility considered by Weiss and Wilkins⁴² only to occur just before death—it leads one to question such an occurrence. The association of a very high alcohol intake over many years with a “certain clinical pattern of heart disease” was so close that it led Brigden⁸ to label 8 out of 50 cases of heart failure due to uncommon myocardial diseases as “alcoholic myocardiopathy”. This condition both clinically and pathologically has certain resemblances to the condition as seen in the Bantu in South Africa. In addition cirrhosis of the liver is frequently encountered in both conditions. Furthermore defective nutrition is common in both instances and therefore both have been called nutritional heart disease.

Resemblances, however, do not indicate identity of ætiology and pathogenesis. No specific deficiency has been conclusively incriminated as an ætiological factor although Gillanders favoured nutritional deficiency in the Bantu cases. He noted improvement followed the institution of a well-balanced diet and claimed that relapse accompanied the reinstitution of a deficient diet. In the Central African variety of cardiomyopathy while chronic liver disease was noted in some of the patients, the possible effects of tropical disease must not be forgotten. Abrahams¹ favours rheumatic fever as a factor, but Davies¹² states categorically that there is no evidence of rheumatic lesions in the vast majority of cases.

In animals necrotic myocardial lesions can be induced by both thiamine and potassium deficiency¹⁷ and such necroses may heal with fibrosis. Perhaps more consideration should be given to the role of K and its relation to Na. Analysis of the basal Bantu diets as used in the metabolism ward showed them to be low in potassium— ± 15 –20 mEq/day. Of interest is the report⁶ of a normal individual who received a diet containing 14 mEq. of K for 55 days and who did not attain K balance. After preliminary sharp losses there was persistent small constant loss in excess of intake which under conditions of prolonged restriction could have led to a severe deficit.

A large positive balance of Na developed (1,102 mEq. when K deficit was 278 mEq.).

Analysis of diets as used in the natural environment may reveal sodium intake to be disproportionately high. Analysis of maize meal porridge prepared by a Bantu woman who added salt to taste revealed a high sodium content (equivalent to as much as 250 mEq./day). The Na/K ratio of that diet was 15/1 instead of a normal value of 3/1.

The disproportionately high Na/K ratio may well be an important factor. The possible lethal nature of the Na ion is borne out by the interesting experiments of Cannon *et al.*¹⁰ on the refeeding of protein-depleted rats. An amino-acid mixture with Na and K or only K resulted in rapid growth and activity, but the combination of high Na and low K resulted not only in failure to grow, but rapid death with the development of severe fulminating necrotic myocardial lesions. The lesions encountered were extensive diffuse or focal areas of hyaline or coagulative necrosis of muscle fibres which differed from the usual K deficiency necrosis. They were located typically subendocardially.

The above findings in animals cannot be readily transferred to man, but they do at least suggest yet another possible mechanism for the genesis of obscure heart failure. Thus in the case of the Bantu the diet with its low K and N₂ content coupled with a continuing renal loss of K it is conceivable that mild potassium depletion may develop, and any further loss is likely to produce major depletion. From time to time there is some restoration of the K stores with the infrequent ingestion of meat or vegetable. Intercurrent infection, trauma, and more particularly episodes of diarrhoea and vomiting will accentuate any depletion of K. Quite apart from the possible effects of K depletion itself the deleterious effects of a high Na intake under these circumstances needs to be considered not only with regard to myocardial function but also the possibility of the production of focal lesions which, when recurrent, might be associated with intractable heart failure.

An interesting recent clinical, electrocardiographic and autopsy study by Smythe *et al.*³⁷ concerns the heart in kwashiorkor. They believe there is clinical evidence of a low-output state, and that the increase in cardio thoracic ratio, the ECG changes and the low weights of the heart found at autopsy indicate that there is wasting of heart muscle. They confirmed the ECG findings of hypokalaemia that have been described in kwashiorkor, but they noted profound ECG changes some of which had not previously been

described during the recovery period and appear to resemble some of the changes described in the adult Bantu. The ECG abnormalities may persist for as long as 6 weeks. While there is no definite evidence of heart failure as being the cause of death in kwashiorkor, enough evidence of disturbed cardiac function has been found to suspect that the heart may play some part in some fatal cases. They felt that there were histological and ECG similarities between some cases of kwashiorkor and the so-called nutritional heart disease of the Bantu. Thus 4 cases showed oedema of the myocardium, undue vascularity and congestion of blood vessels, relative hypertrophy or atrophy of muscle fibres of the left ventricles.

The actual genesis of obscure heart failure in the Bantu is still unsolved but a multiplicity of factors is likely and these may include, *inter alia*, protein and vitamin deficiencies and electrolyte disturbance. These have all to be considered in relation to an individual who is often, perforce, a heavy manual worker. Under these circumstances the demands on a possibly defective myocardial metabolism may be excessive and may lead to further deterioration.

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CHAPTER 20 (*Contd.*)

ABNORMALITIES OF FLUID AND ELECTROLYTE METABOLISM IN MALNUTRITION IN INFANTS

by

J. D. L. HANSEN

Physiology of Water and Electrolytes in Infancy and Childhood

IN 1951 Gamble,¹² in his classic Lane Medical Lectures, summarized his work on the structure of the body fluids and drew attention to the essential differences between adults and infants in water and electrolyte metabolism. A fact stressed by him and of great clinical importance is that the body surface of an infant is about twice as great as that of an adult per unit of body mass. The basal insensible loss (evaporative loss) is therefore relatively twice as large. Also as the basal metabolic rate is proportionate to surface area, a relatively larger quantity of substances presents for removal in the urine with a corresponding increase of the renal water requirement. The obligatory water loss—composed of the relatively small loss in the stools, the basal insensible loss and the minimum renal expenditure—works out at approximately 300 ml. for a 7 kg infant and 1,400 ml. for a 70 kg. adult. The infant therefore has one-fifth the expenditure of the ten times larger adult and will have a shorter survival expectancy in the presence of circumstances which prevent or limit water intake.

In health the water exchange of an infant provides a large margin of safety. The natural food, milk, provides a daily volume of intake approximately twice that of the obligatory expenditure and is equal to one-half of the extracellular water content of the body. In contrast the adult drinks about one-seventh the volume of his extracellular fluid during 24 hours.

In a meticulous study Friis-Hansen¹⁰ has experimentally defined total body water, intra and extracellular fluid volumes at various ages during infancy and childhood. This information is of great importance now that studies of body composition in health and

disease are becoming practicable. The actual figures determined are as follows:

Age	Total body water % body weight	Extracellular fluid % body weight	Intracellular fluid % body weight
0-11 days .	77.6	41.6	34.8
11 days-6 mths .	72.2	33.7	37.9
6 mths.-2 yrs. .	59.5	26.2	34.7
2 yrs.-7 yrs. .	63.1	24.7	39.9
7 yrs.-16 yrs. .	58.4	19.9	46.7

The changes found in body water compartments, in per cent of body weight, during growth, may thus be described as a rapid decrease of total body water during the first year of life, with a similar decrease of extracellular water, whereas intracellular water remains practically constant. A slight increase of all three compartments is then observed from one to two years of age. During the later part of childhood a continuous decrease of extracellular water is found whereas only minor changes of total and intracellular water are seen. The significance of these changes may be described as: (1) a relative increase in the proportion of cells in most tissues at the expense of extracellular fluid; (2) a disproportionately higher development of such organs as muscles that have a high proportion of intracellular water; and (3) a varying amount of fat tissue in the body.

In recent years more data has been collected on the quantities of water and electrolytes lost from the skin under various conditions. Thus normal infants lose 1-1.5 mEq. each of sodium, potassium and chloride from the skin every 24 hours under conditions that lead to minimal or no visible sweating.⁶ These quantities can be greatly increased when temperatures go above 81° F. and in another publication Darrow⁸ has recorded losses of water in the sweat to be as high as 50-100 ml./kg./day. During the development of dehydration in high environmental temperatures losses of water in sweat can therefore be quantitatively as important as losses from diarrhoeic stools. (See later.)

Likewise the role of the lungs in water balance is of great importance. There is an approximate linear relationship between the minimum daily water loss from the lungs and the body weight. In the newborn infant the minimum daily water loss from the lungs is between 6 and 12 g./kg.^{20, 33} Placing the infant in a supersaturated atmosphere will reduce the water loss by this route.²⁶ It has been

estimated that during hyperventilation and fever the basal water loss from the lungs may rise from 75 to as much as 1,000 ml. of water per day, or, expressed in terms of body weight, 20 per cent per day.²⁶ These figures are quoted to illustrate a few of the factors that must be taken into account when planning diets of children under varying environmental conditions and clinical states.

In health the average stool weight of children aged 1–6 years is approximately 100 g./day with a negligible loss of electrolyte.²³ In diarrhoea stool weights rise to 300 g./day or more and can produce losses of water as high as 50–85 ml./kg./day.⁸ Average deficits of sodium, potassium and chloride are respectively 9, 9 and 10 mEq./kg. in the dehydrated infant.⁸

Dietary Causes of Electrolyte and Water Imbalance

During Health. Increase in renal solute load, e.g. the use of unmodified evaporated milk mixtures in infant feeding, can decrease the margin of safety against dehydration under conditions of large extrarenal water losses in sweat and from the lungs.²⁷ Also any inadvertent excessive intake of salt to infants may lead to anorexia and vomiting and hypernatræmic dehydration.¹⁷

During Treatment of Disease States. (1) *Interference with Oral Intake of Water.* Anorexia or neglect of water administration to sick infants may lead to hypernatræmic dehydration¹⁷ (i.e. serum sodium concentration more than 150 mEq. per litre). This occurs in particular in febrile states, as a result of salicylism and when there are other causes of hyperventilation.²⁸

(2) *Excessive Administration of Electrolytes or of Protein to Sick Infants.* Colle *et al.*⁵ have drawn attention to the ease with which hypernatræmic dehydration can occur from unnecessarily high intakes of protein and electrolytes during treatment of diarrhoea. They emphasize how important it is to assess children clinically and not to rely always on standard electrolyte solutions without giving proper attention to water requirements.

(3) *Insufficient Administration of Electrolytes in Salt-Losing States.* Hyponatræmic states may occur where water, e.g. 5 per cent dextrose water, is used as a sole rehydrating solution in conditions such as diarrhoea, vomiting, loss of fluid from ileostomy or colostomy, and conditions such as the adrenogenital syndrome, pancreatic fibrosis, salt-losing nephritis, cerebral salt-wasting states.¹⁹ Water intoxication with convulsions can easily occur under these conditions if insufficient attention is paid to salt loss and its proper replacement.

Electrolyte and Water Imbalance in Association with Nutritional Deficiencies of Infancy and Childhood

Imbalance of water and electrolyte metabolism in nutritional disturbances of infancy and childhood (e.g. marasmus and kwashiorkor) must be considered in relationship to the diarrhoea that so frequently precedes or accompanies these syndromes.^{4, 29, 31} McCance²² has also commented on the frequent association of diarrhoea and hunger oedema in adults. Objective quantitative studies of losses of nutrients in the stools of cases of kwashiorkor have recently confirmed the importance of malabsorption in this syndrome. Thus decrease in apparent absorption of nitrogen is a striking finding in the early stages of treatment of kwashiorkor.^{7, 15, 18} This malabsorption applies also to electrolytes.¹³ The 24-hour stool weights of cases with kwashiorkor have been found to be three to four times that of normal children (200–300 g./day) even in the absence of severe diarrhoea as judged clinically.¹⁶ These high stool weights mean that water loss by this route can also be of considerable magnitude in nutritional disorders.

The composition of the diet especially with regard to water and mineral content will in large part determine the pattern of water and electrolyte disturbance in cases of malnutrition. Balance studies in cases of kwashiorkor with oedema have suggested that there is an excess accumulation of water, sodium and chloride in the body and an overall deficiency of potassium.¹³ Diuresis is accompanied by a large loss of sodium and chloride and there can be as much as a 17 per cent loss in body weight indicating the degree of excess total body water during the oedematous phase. More recent studies of body composition in kwashiorkor have indicated that conclusions drawn from the balance studies were largely correct. Thus Schnieden and co-workers³⁰ have demonstrated an increase in total body water by measurement of the deuterium space. Frenk *et al.*¹¹ showed that skin and muscle had an increase of total content of water, sodium and chloride while at the same time there was a low content of potassium. The same workers in a further publication²⁴ feel that there is extracellular hypotonicity and intracellular overhydration in kwashiorkor. However, extracellular hypotonicity is not always present¹³ and much must depend on the salt content of the diet as to whether hyper or hypotonicity of the extracellular fluid develops.

Muscle biopsy of cases in the West Indies showed that in addition to decrease of muscle mass, there is a decrease in phosphorus and

potassium content of muscle even in non-œdematous cases.³⁵ These workers also found an increase of water content in the muscle and presumed that most of the increase was extracellular. These studies in the West Indies have been extended recently to the measurement of total exchangeable potassium in infantile malnutrition. It was found that exchangeable potassium is 25–30 per cent reduced in chronic malnutrition and that the serum potassium level which is often low in kwashiorkor is no guide to the extent of potassium depletion.³² The same group of workers claim that magnesium deficiency in malnutrition parallels potassium deficiency.²⁵ This latter finding agrees well with the suggestive association of states of malabsorption with magnesium deficiency.⁹ It is of interest that correction of mineral deficiencies, particularly of potassium, can in certain cases lead to a diuresis even in the absence of a protein intake or change in serum albumin concentration.¹³

The role of the adrenal cortex and other endocrine glands in the development or modification of the above-described abnormalities of water and electrolyte metabolism is discussed in Chapter 27.

Correction of Water and Electrolyte Imbalance in States of Malnutrition

The principles of treatment are essentially similar to those applied generally in pædiatrics. There have been many advances in this field and the most modern approach to therapy is covered in detail by a panel of experts in a recent symposium.³⁴ Calculation of fluid requirements on a body surface basis is advocated by some workers.²

The correction of dehydration and electrolyte imbalance is probably the most important part of the initial therapy of kwashiorkor and marasmus. The frequent association of diarrhoea and malabsorption with these two syndromes requires careful management by the clinician.

A simple scheme adopted by the author¹⁴ has been found of great value in practice when dealing with large numbers of dehydrated children, many of whom are severely malnourished.¹ Total fluid requirements over the first 24 hours are calculated as follows:

- (1) Replacement Fluid: 5–10 per cent of the body weight (50–100 ml./kg.) depending on degree of dehydration;
 - (2) Maintenance Fluid: 120–150 ml./kg., e.g. 10 kg. child severely dehydrated
- | | |
|--------------------|-----------|
| Replacement fluid | 1,000 |
| Maintenance fluid | 1,500 |
| Total 24-hr. fluid | 2,500 ml. |

Half isotonic Darrows solution is used as a standard replacement and maintenance fluid under these circumstances. This solution supplies 60 mEq. of sodium, 17 mEq. of potassium, 50 mEq. of chloride and 25 mEq. of lactate/litre, and is safe when given in the quantities prescribed over a 24-hour period. In busy clinics there is a great advantage from the point of view of the staff in using one standard solution for oral and intravenous therapy. Where laboratory facilities are available more water or more electrolyte may be prescribed in instances where there is hyper or hypotonicity respectively. Similarly in children where there is complete anuria it may be desirable to use isotonic saline or Ringer lactate in place of Darrows solution until urine is secreted so as to avoid a too rapid rise of serum potassium. In general, however, there is such a significant degree of potassium depletion in malnourished children that early administration of potassium is essential.

It is preferable to administer fluids *intravenously* by scalp vein infusion if there is any significant degree of dehydration. The great value of this even in cases which are oedematous, has been demonstrated by Kahn²¹ who showed that introduction of intravenous therapy halved the mortality rate in cases of kwashiorkor. In children who are not dehydrated, oral therapy will usually suffice and in these instances replacement fluid should not be prescribed.

When rehydration has been accomplished, usually within 24–36 hours, oral dietetic therapy is commenced. In the presence of continuing severe diarrhoea, supplementary intravenous administration of fluid and electrolyte should be continued, using always half isotonic Darrows solution in quantities calculated on replacement requirements. (See above.)

In dietetic therapy the principles enunciated by Chung³ are finding favour. He has found that by increase of feeding in diarrhoea there is a greater absolute absorption of nutrients.

Undiluted skim or full-cream milk should be introduced early into the diet. Increase in number and volume of stools will frequently result but this development should be ignored if there is no vomiting and the child remains hungry. Long-continued withholding of milk on the ground of the persistence of loose stools is seldom justified and can only lead to further malnutrition and weakness of the patient.

Mineral Supplements

Potassium chloride $\frac{1}{2}$ g. t.d.s. should be given for at least 10 days to help correct potassium deficiency.³² It is possible that supplements

with magnesium in the form of magnesium hydroxide by mouth or magnesium sulphate by injection will prove to be helpful.⁹

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CHAPTER 21

NUTRITION RESEARCH IN SPANISH- PORTUGUESE SPEAKING COUNTRIES

by

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THE present review will be primarily concerned with advances in nutrition in Latin America, but an effort will be made, because of similarities in language and tradition, to call attention to work done in Spain and Portugal.

In most of the Latin-American countries, mortality under 1 year and in the 1-4 year age groups is high¹ and there is considerable evidence that malnutrition is a major factor. The available information on cause-specific death rates also suggests this conclusion.²⁻⁵ A disproportionately high birth rate resulting in an extremely rapid population growth is another complicating factor which should receive careful attention since it is likely to aggravate prevailing conditions and make already insufficient food supplies even more inadequate. Fortunately, governmental and other agencies have begun to realize that urgent action is needed to change a rudimentary agriculture, food industry and economy into a modern and efficient system satisfactory for meeting the demands of the increasing population. Nutritional research has been recognized as essential to assess the *status quo* and establish the present needs in specific terms as a basis for finding practical ways of overcoming existing deficiencies and satisfying future demands.

In Latin America, the Pan American Health Organization (PAHO), regional office of the World Health Organization (WHO) for the Americas, and the Food and Agriculture Organization (FAO) have stimulated interest in nutrition research and in applied nutrition programmes. They have jointly sponsored conferences on nutrition

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problems in Latin America, in Montevideo in 1948,⁶ Rio de Janeiro in 1950,⁷ Caracas in 1953⁸ and Guatemala in 1957,⁹ as well as area seminars on nutrition education. These organizations also provide consultants to help solve local nutritional problems and promote nutrition research. The regional and area conferences and travel grants for research workers have resulted in a greater exchange of ideas and a better understanding of nutrition problems.

The lack of technically trained personnel has been a major handicap to sound nutrition research in Latin America. However, in the past decade, organizations such as WHO, PAHO, FAO, UNESCO, ICA, the W. K. Kellogg Foundation, the Rockefeller Foundation, and the Guggenheim Foundation, have helped alleviate this situation by providing for the advanced training of a number of nutrition workers. Some organizations also contribute additional funds for purchasing the equipment and supplies used for both research and applied work. The lack of trained technicians should become less acute as well-oriented training and fellowship programmes continue; reintegration of fellowship recipients into faculties of local universities is beginning to facilitate advanced training at the local level.

The fact that nutrition institutes have been established in Argentina, Brazil, Central America, Colombia, Ecuador, Mexico, Peru and Venezuela, and that the health departments of most of the other countries have set up nutrition sections or divisions, is a clear indication that nutrition problems are now widely recognized in Latin America. The Institute of Nutrition of Central America and Panama (INCAP), is an excellent example of what countries of limited resources may achieve through co-operation to provide for their research and consultation needs.

Most nutrition institutes in Latin America actively follow the recommendations of the regional conferences on nutrition problems. They have been initially concerned with the food analyses necessary for the elaboration of food composition tables, and the dietary and clinical surveys required for the accurate assessment of dietary habits and nutritional status. Considerable attention has also been devoted to specific problems such as endemic goitre and severe protein malnutrition in children. Food analyses continue, but more for the purpose of finding new food sources and formulating suitable high-quality protein vegetable mixtures to help solve the widespread problem of protein malnutrition.

The lack of effective communication of results has retarded progress and often caused expensive duplication of efforts. At present, unless results are published in journals outside the area, they are

likely to be missed in a local publication of scanty circulation, frequently not reviewed by international abstracting services. The Fourth Conference on Nutrition Problems in Latin America,⁹ recognized this problem and strongly recommended the publication of a special journal devoted exclusively to the nutrition work in the area. While this has not yet been done, Archivos Venezolanos de Nutrición has recently added an international section for the specific purpose of publishing original research reports in the region.

Nutritive Value of Foods

Beginning in 1942, numerous food composition tables have been published in Latin America. The work of the pioneers, however, was greatly handicapped by lack of uniformity in procedures. In addition, analytical methods were not available for the quantitative determination of some important nutrients. The specific recommendations of the Second Latin American Nutrition Conference⁷ have encouraged the standardization of both analytical and computational procedures.

The interest of Dr. Robert S. Harris of the Massachusetts Institute of Technology (MIT) in the composition of foods in Latin America, has resulted in the preparation of fairly complete food composition tables. His influence is particularly evident in food analyses reported in Mexico,¹⁰ Guatemala,¹¹⁻¹³ El Salvador,¹⁴ Honduras,^{15, 16} Nicaragua,¹⁷ Costa Rica,¹⁸ Cuba,^{19, 20} and Ecuador.²¹ Latin-American biochemists trained at MIT to carry out some of these analyses, later extended them, and now comprehensive food composition tables are available for most countries.

In Argentina, the original tables published in 1942,²² were supplemented in 1945 with determinations of the vitamin content of edible vegetables.²³ In 1950, Kemeny²⁴ prepared a food composition table for Chile, and the Institute of Nutrition of Central America and Panama, compiled a provisional food composition table for Central America and Panama.²⁵ Successive editions were published by INCAP in 1951,²⁶ and 1953.²⁷ A supplement in 1955 listed additional analyses,²⁸ added a section for animal feeds,²⁹ and included a glossary of common local food names.³⁰ A considerably expanded and improved fourth edition of this table has recently appeared.³¹

A food composition table for Mexico, including the analyses in 817 different food samples, was published in 1951 by Cravioto *et al.*³² In 1953, Góngora y López and Young³³ prepared a food composition table for Colombia, and the same year, the Home Economics Department of the University of Puerto Rico issued a mimeographed food composition table.³⁴ In 1954-5 food composition

tables were published by the National Institute of Nutrition of Venezuela,³⁵ and the "Fundación de Investigaciones Médicas" (FIM) of Cuba.^{36, 37} A table incorporating available previous information was also distributed in 1957 by Collazos *et al.* of the National Institute of Nutrition of Peru.³⁸ The National Institute of Nutrition of Ecuador expanded the information made available by Munsell *et al.*,²¹ and issued successive food composition tables in 1957 and 1958.^{39, 40}

Reports on food composition are available for Spain^{41, 42} and the Portuguese colonies of Mozambique, Angola, Timor, Zambesi and Congo.^{43, 44} Analyses for the content of various specific nutrients are also available for many of the Latin-American countries.⁴⁵⁻⁵¹ Because of their importance as staples or their potential industrial value, fish,^{52, 53} fish flour,⁵⁴ fish eggs,⁵⁵ the Brazil nut,⁵⁶ corn,⁵⁷ legumes,⁵⁸ the seeds of certain varieties of *Cucurbita pepo*⁵⁹ and fruits,⁶⁰ have received special attention.

As methods for amino-acid determinations became available and more widely used, some reports began to include data on the amino-acid content of selected foods.⁶¹⁻⁶³ Recognition that the basic nutrition problem was lack of adequate protein, resulted in measurements of essential amino-acid deficiencies in staple vegetable foods.⁶⁴⁻⁶⁹ This information led to studies of the effect of amino-acid supplementation^{70-74, 84} and the use of complementary protein sources to improve dietary protein quality.⁷⁵⁻⁷⁷ In Brazil,^{78, 79} Mexico⁷⁵ and Venezuela⁸⁰ powdered milk has been studied as a complement to vegetable diets, while fish flour has been tried in Chile⁸¹ and Mexico⁸² with apparently satisfactory results.

Workers in the Children's Hospital of Mexico have published excellent studies of the nitrogen metabolism of children fed mixtures of corn and beans supplemented with milk⁷⁵ and fish flours.⁷⁶ Their studies of the effectiveness of vegetable and animal proteins in supplemental feeding programmes are of particular interest.⁸⁶

An approach stressed by INCAP in Central America is the formulation of vegetable mixtures with complementary amino-acid content to give a better net protein value.⁸³ Working with corn, sorghum and cottonseed flour, this group devised a formula for a vegetable mixture which not only results in nitrogen retentions in children comparable to those obtained with milk or other high quality protein sources,⁷⁷ but also is effective in the treatment of kwashiorkor.⁸⁵ This mixture, called "Incaparina", has proved acceptable to the population for whom it was developed, and costs approximately 1 cent (US) for a glass containing 7 g. of protein and a

balanced content of other nutrients. Studies of vegetable protein for child feeding are now also in progress in the National Institute of Nutrition of Peru, but no published reports have yet appeared.

The preceding discussion gives evidence that there is ample information, though scattered, concerning the composition of foods in Latin America. The Fourth Conference on Nutrition Problems in Latin America⁹ recommended that all available information be organized and compiled into a food composition table for the area. The Interdepartmental Committee on Nutrition for National Defense (USA), which faced this problem in carrying out nutrition surveys in other areas, is now co-operating in a joint project with the Pan American Health Organization through the Institute of Nutrition of Central America and Panama, in the preparation of a food composition table for Latin America. This project is progressing rapidly and the report should be available late in 1961.

Assessment of Nutritional Status

When the First Conference on Nutrition Problems in Latin America was convened in Montevideo in 1948,⁶ information concerning diet and dietary habits was available for a few countries in the area.⁸⁷⁻⁹² However, it was recognized that this information, without parallel chemical and laboratory data, would not permit an objective assessment of nutritional status. The conference recommended, therefore, "that surveys of the *state of nutrition* should be made to obtain a better picture of the situation of populations in the region".⁶ Following this conference, the nutritional conditions among population groups in Brazil,⁹³⁻⁹⁵ Chile⁹⁶ and Argentina⁹⁷⁻⁹⁹ were studied, but these emphasized the economic aspects of the diet and neither clinical nor laboratory data were included.

In 1950, the Second Conference on Nutrition Problems in Latin America,⁷ specifically recommended the standardization of dietary survey methods to permit the direct comparison of results from different areas. The conference also considered the question of the evaluation of nutritional status, suggesting again that diet surveys alone would not suffice for this purpose. For the assessment of nutritional status, parallel clinical surveys to determine the relative frequency of carefully defined deficiency signs, along with laboratory determinations such as hæmoglobin and hæmatocrit, were stated to be a necessary complement of dietary surveys. The availability of ultra micro-methods for the determination of serum alkaline phosphatase, vitamin A, carotene, vitamin E, ascorbic acid and riboflavin in less than 1 ml. of blood, led to their use in survey work.

The conference, however, recognized the difficulties involved in these laboratory procedures. It suggested that height and weight data for the evaluation of growth and development should be accompanied, whenever possible, by suitable X-ray studies which would permit the assessment of bone maturation.⁷

Bengoa, of the National Institute of Nutrition in Venezuela, prepared a series of reports¹⁰⁰⁻¹⁰⁷ summarizing dietary information for Venezuela. The inventory technique was used for a 7-day period, although balance sheets were utilized when considering the problem on a national basis. In general, all of these studies indicated that the riboflavin, niacin, thiamin, vitamin A and fat intakes were low, ranging from 50-66 per cent of the recommended dietary allowances of the National Research Council (U.S.); protein intake averaged 79 per cent while calcium and caloric intakes averaged 70 and 85 per cent respectively of the recommended allowances.^{100, 106} The diets contained other nutrients in adequate amounts. These reports incorporated some clinical and laboratory information¹⁰⁴ and frequently referred to economic factors influencing the diet^{101, 102, 107}; special attention was given to the study of conditions in rural communities.^{103-105, 107} In 1950 Liendo Coll¹⁰⁸⁻¹¹⁰ summarized the ideas of the National Institute of Nutrition of Venezuela concerning the clinical evaluation of nutritional status.

Clinical surveys independent of the dietary surveys summarized above, revealed signs suggestive of vitamin-A deficiency in 64 of 101 school children examined in Caracas; evidence of riboflavin and nicotinic acid deficiency was also observed. Red cell count was below and hæmoglobin concentration was above normal in these children.¹¹¹ Similar clinical findings were reported in a study of 221 working-class adults.¹¹²

The first report of dietary findings for the Central America region was published in 1951 by Reh, Benitez and Flores.¹¹³ In subsequent dietary surveys, parallel clinical and laboratory investigations were included, and height and weight measurements were supplemented with wrist X-rays for the evaluation of bone maturation. In general, the dietary surveys which followed a 7-day direct interview method¹¹⁴ indicated a low intake of protein from animal sources, and of riboflavin and vitamin A.¹¹⁵⁻¹²² Clinical surveys in school children revealed growth retardation ranging from 2 to 3 years in both height and weight¹²³⁻¹²⁶ and bone maturation,¹²⁷ presumably due to a low protein intake. The widespread occurrence of the "Síndrome Pluricarenal de la Infancia" (SPI, kwashiorkor) in the area¹²⁸ is additional clinico-pathological evidence of the serious dietary

deficiency of protein of animal origin. Laboratory findings indicated heavy parasite infestation as well as a tendency to macrocytosis.¹²⁹⁻¹³² Serum protein values were within the range considered normal, but they did not reflect the protein deficiency evidenced in the dietary and clinical studies and are considered of little value for survey work.¹³³ Serum vitamin-A findings¹³⁴ paralleled the dietary findings, although the clinical evidence for this deficiency was considered of doubtful significance.¹³⁵ A recent survey in pre-school children¹³⁶⁻¹³⁷ which included dietary, clinical and laboratory information, gave similar results. The protocol, used in all the clinical surveys in Central America, has been described in detail by Muñoz and Percz.¹³⁸

The National Institute of Nutrition of Ecuador described the prevailing nutritional situation in the country through data derived from dietary surveys conducted in 1953 in five areas. In general, the results indicate a deficient calcium intake in all the localities studied; riboflavin intake was low in four of the communities while the vitamin-A intake was considered adequate only in two coastal communities included in the study. Total protein intakes were generally adequate, but the proportion of animal protein in the diet was low. Although no parallel clinical and laboratory data were obtained in the course of these surveys, a relatively frequent occurrence of clinical signs suggestive of vitamin-A and riboflavin deficiencies was observed; no evidence of calcium deficiency was reported.¹³⁹

Recent height and weight studies in 1,200 school children of both sexes attending private schools in Guayaquil, give no evidence of any growth retardation as judged by these criteria¹⁴⁰; the children included in these studies, however, do not correspond to the population groups included in the dietary surveys. Extensive clinical surveys were conducted in Ecuador in 1958, but no published reports are yet available.

Nutrition research in Peru seems to have begun after the First Conference on Nutrition Problems in Latin America in 1948. At this time, the Peruvian delegation reported activity in the field of nutrition in connection with feeding programmes for school children and workers and their families.⁶ An early report¹⁴¹ indicates that the diets consumed by the Peruvian Indians are low in protein, calcium, iron and vitamins, but makes no reference to specific vitamin deficiencies. Additional general information is available, particularly for the dietary habits and nutritional situation of selected groups of population,¹⁴²⁻¹⁴⁶ but a clearer picture of the nutritional status in

Peru is presented in the published reports of the National Institute of Nutrition.¹⁴⁷⁻¹⁵³

The dietary surveys conducted in representative areas by the above group revealed deficient intakes of calcium and riboflavin, low intakes of vitamin A and thiamin, and intakes of protein somewhat below desirable levels. Dental caries was extensive, muscular development frequently poor and clinical signs possibly related to nutritional deficiencies, particularly of vitamin A, were common. In addition, there was a high prevalence of intestinal parasites, and anaemia was widespread.¹⁴⁷⁻¹⁴⁹

A recent study¹⁵⁴ has identified the moderate anaemia in heavily parasitized children living in Peruvian jungle towns as a macrocytic, hypochromic type, probably due to nutritional factors. Studies of weaned children up to 3 years of age in a cotton plantation, a fishing village and a jungle town, indicate that the diets of these children are commonly low in calcium, vitamin A, riboflavin, protein and iron. There were indications that parasitic infestation was common, and there was evidence of growth retardation.^{150, 151} In the jungle town, no child examined was entirely free of signs possibly related to nutritional deficiency, but no correlation could be established with dietary intakes.¹⁵¹ Growth and development studies indicate that the children living in these communities are below normal for age, especially in height, compared to North American standards. Both "developmental age" (Wetzel) and skeletal age as determined from X-ray studies of hand and wrist were also retarded in relation to chronological age.^{152, 153}

Thonnard-Neumann¹⁵⁵ in a 1957 review, finds the diet of the well-to-do in Colombia to be adequate, and the food consumption of the lower socio-economic classes to be generally low in both quantity and quality; he states, however, that an excess of fat is consumed by all groups. Children are light and short, and it is stated that 90 per cent of the children are affected by iron-deficiency anaemia. A macrocytic, megaloblastic anaemia with nerve involvement but without achylia which occurs in adults, is reported to respond better to treatment with crude liver extracts or folic acid than to treatment with vitamin B₁₂. Deficient intakes of protein result in kwashiorkor in children, but no protein-deficiency signs are seen in adults. Vitamin-A deficiency accompanied by Bitot spots is very common. Beri-beri is rare and pellagra, although not found in the coastal areas, is present in mild form in corn-consuming areas in the interior. Riboflavin deficiency accompanied by angular stomatitis is common. Changes in adolescents at the costochondral junctions and femoral

epiphyses are attributed to vitamin-C deficiency. Rickets are rare but the dietary intake of calcium is generally insufficient. "Tropical diseases and malnutrition" are held responsible for liver damage by this author. The results of dietary surveys conducted by the "Servicio de Asistencia Social" and the National Institute of Nutrition in co-operation with FAO,¹⁵⁶ suggest diets low in calories, calcium and riboflavin. The results of other surveys by Flores¹⁵⁷ and Esquef¹⁵⁸ in different areas of Colombia have not yet been published.

De los Cobos *et al.*,¹⁵⁹ in a study designed to evaluate a child feeding programme in Tlaxcala, Mexico, described diets for children under 5 years of age low in riboflavin, niacin and vitamin C, and apparently adequate in protein, calories, calcium, iron and thiamin. A group of children in the same locality and similar socio-economic status from 5 to 15 years of age, had low intakes of calories, protein, riboflavin, niacin and vitamin C. Protein from animal sources was particularly low in this group, constituting only about 6.1 per cent of the total protein intake. There is evidence of growth retardation, but the only clinical evidence suggestive of malnutrition was bleeding gums, which the authors believed related to the extremely low vitamin-C intakes. Total serum proteins were within the lower normal range. Serum albumin was low and both alpha-globulin and gamma-globulin were high. The findings are stated to agree with others for Mexico.

Segovia,¹⁶⁰ in a study designed to evaluate the biological value of the "Mean National Diet" in Chile (Dieta Estadística Nacional, DEN), reports adequate protein content for N balance in rats. An improvement in the growth of rats was evident, however, when the DEN with 12.8 per cent protein was supplemented with 8.5 or 11.8 per cent milk, but no gain was observed with the addition of 0.10 per cent DL-methionine. An improvement equivalent to that observed with the addition of milk could be obtained through the addition of calcium alone in the same proportion as in the 8.5 per cent milk supplement. On this basis, the author concludes that the DEN is primarily limiting in calcium. Similar studies have indicated that the Chilean diet is also low in iron, but failed to confirm dietary survey findings of low thiamin, riboflavin, vitamin A and nicotinic acid. The addition of vitamin B₁₂ to the DEN did not enhance its biological value as determined by growth studies.

A dietary survey in the Santa Cruz area of Bolivia¹⁶¹ indicated low intakes of calcium, riboflavin, thiamin and vitamin A. In some cases evidence was found of deficient intakes of calories, protein and iron.

Family diets of labourers were, in general, more limiting than diets consumed by the farm owners and by urban households. The diets consumed by children 1-4 years of age compared less favourably with NRC recommended allowances than the diets consumed by other members in the household.

In Brazil, evidence of protein deficiency is manifested through the common occurrence of kwashiorkor.¹⁶² Different surveys have also revealed iron, calcium, vitamin A, vitamin C and B-complex deficiencies.^{163, 164} Some areas of the country are more affected than others because of predominant agricultural monocultivations,⁹⁵ or because special climatic conditions such as droughts have repeatedly aggravated the prevailing conditions and have precipitated severe nutritional deficiencies.¹⁶⁵

It is evident that nutritional deficiencies affect a sizeable proportion of the Latin-American population, particularly young children of pre-school age and pregnant and lactating mothers. Gomez of Mexico, dramatically summarized his personal observations of the serious nutritional problem in the area in a 1950 editorial, stating that less than half of the population of Latin America obtains as much as 65 per cent of its caloric requirements, that the protein content of diets is generally low and of poor quality, and that vitamin deficiencies are commonly associated. Although he considered xerosis, oedema and pellagra to be less common than might be expected, subclinical evidence of extremely poor nutrition abounds.¹⁶⁶ The truth of this appraisal is constantly being confirmed.

More complete information concerning the nutritional status of the population in Latin America should be available when the reports of integrated surveys including dietary, biochemical and clinical information, conducted by the ICNND* in Peru and Ecuador, and now under way in Chile and Colombia, are completed.

Nutritional studies in Spain suggest growth retardation, calcium and protein deficiencies to be prevalent among children of low socio-economic status,¹⁶⁷ although the deficiencies do not seem to be uniformly distributed in all the Spanish peninsula. Studies in some rural areas give no evidence of growth retardation or other deficiencies,¹⁶⁸ but sporadic cases of rickets^{169, 170} and kwashiorkor^{171, 172} are reported from certain areas.

Studies in Portugal suggest diets low in calcium and protein from animal sources in one of two rural localities studied, while in the other the diet was low in calcium and riboflavin, but apparently adequate in protein. Dental lesions and malformation, skeletal

* Interdepartmental Committee on Nutrition for National Defense (U.S.A.).

malformations and physical underdevelopment were the most common clinical observations.¹⁷³ A survey among workers in a factory indicated the presence of signs associated with rickets (costochondral rosary). Different types of dental lesions were very common as was the vascularization of scleral conjunctiva. Also observed, though less frequently, were hæmorrhagic gingivitis, glossitis and alveolar infection.¹⁷⁴ In a preliminary report, Janz¹⁷⁵ states that pellagra is endemic in the northern and two central areas of Portugal where corn is apparently consumed. Skin lesions are the most frequent signs, but digestive, mental and nervous symptoms of pellagra were also reported.

Endemic Goitre

The seriousness of endemic goitre as a public health problem in the Latin-American countries is being recognized with the increasing availability of data regarding its prevalence. The condition is known to be widespread in Bolivia,¹⁷⁶ Colombia,¹⁷⁷ Costa Rica,¹⁷⁸ Ecuador,¹⁷⁹ El Salvador,¹⁸⁰ Guatemala,¹⁸¹ Honduras,¹⁸² Mexico,¹⁸³ Nicaragua,¹⁸⁴ Panama,¹⁸⁵ Paraguay,¹⁸⁶ Peru,¹⁸⁷ and Venezuela,¹⁸⁸ as well as in certain areas of Argentina,¹⁸⁹ Brazil,¹⁹⁰ Chile,¹⁹¹ and Uruguay.¹⁹² No statistics have yet been given for the Dominican Republic, Cuba or Haiti, but endemic goitre is probably not important in the Caribbean Islands.

The four joint FAO-WHO Conferences on Nutrition Problems in Latin America⁶⁻⁹ stimulated interest in this problem. The Third Conference, held in Caracas, Venezuela, in 1953,⁸ summarized in detail the present knowledge recommending more studies about prevalence, and the enactment of legislature for the iodization of salt in those countries where endemic goitre is prevalent.

In general, the prevalence of endemic goitre increases with altitude,¹⁸¹ although there are some coastal areas of high endemicity.¹⁸⁵ Goitre is more prevalent during puberty,¹⁸⁵ and its frequency is usually greater in females than in males.¹⁸¹ Most of the surveys have been made on school children because they are easier to examine and are considered a good indicator of the recent extent of the problem. Some communities have a goitre prevalence of over 80 per cent.¹⁸¹ Feeble-mindedness, deafmutism and cretinism have been associated with endemic goitre in nine Latin-American countries,⁸ although no causative relationship between the two conditions has been demonstrated. No reliable reports on the frequency of thyrotoxicosis and thyroid carcinoma have appeared.

It is accepted that endemic goitre is produced by relative iodine

deficiency in the diet, although the effect of goitrogenic factors on relative iodine requirements has not been investigated in Latin America. The effectiveness of iodine administration, either as potassium iodide or iodate in salt, or tablet form, has been clearly demonstrated in Colombia,¹⁹³ Guatemala and El Salvador,¹⁹⁴ and Spain.^{195, 196} Potassium iodate has proved sufficiently stable to be added to crude, moist salt without refining or special packaging.¹⁹⁷ Based on these trials, the Third Conference on Nutrition Problems in Latin America⁸ recommended that potassium iodate be added to crude salt at levels of one part of iodine to 10,000 to 20,000 parts of salt. These levels are considerably higher than those recommended in Europe, but it is felt that they allow for goitrogenic factors as well as variations in salt intake and have been proven safe, economical and effective.

By 1958, Paraguay, Guatemala, Colombia, Costa Rica, Ecuador, Panama and Mexico passed legislation for the compulsory, nationwide iodization of salt, while Argentina, Brazil and Uruguay require it for areas where endemic goitre is a major public health problem.⁹ In 1959, only Paraguay and Guatemala were enforcing these laws, but steady progress is expected throughout Latin America in the enactment of legislation requiring the iodization of salt in additional countries and in the enforcement of such laws.

The first comprehensive report on endemic goitre in Latin America was presented at the Second Conference on Nutrition Problems in Latin America in Rio de Janeiro,⁷ by the "Cooperación de Ventas de Salitre y Yodo de Chile in 1950".¹⁹⁸ Scrimshaw,¹⁹⁹ in 1954, published a review of the same subject, followed in 1958 by Kelly and Snedden's extensive review of the world-wide prevalence of endemic goitre.²⁰⁰ The latest review of endemic goitre in Latin America will appear in September, 1960.²⁰¹

Kwashiorkor

One of the first reports in the world literature of the syndrome now known as kwashiorkor, was that of Patrón Correa,²⁰² who in 1908 published a study of the disease in Yucatán, Mexico, under the name "Culebrilla". In the 1930s, before any published description in Africa, Carrillo²⁰³ in Mexico, Castellanos²⁰⁴ in Cuba, Cofiño and Arguedas Klee²⁰⁵ in Guatemala, Goens Rosales²⁰⁶ in El Salvador, Franco²⁰⁷ in Venezuela and Vidal²⁰⁸ in Honduras, described the syndrome using names such as "síndrome pelagroide-beribérico", "Caquéxia hídrica infantil", "edema avitaminósico de la infancia" or "Síndrome Policarencial". Although these authors did not yet

recognize the specific role of protein in the disease, they believed it to be due to multiple nutritional deficiencies, especially of vitamins.

In 1944 Flores²⁰⁹ gave an account of the clinical features, ætiology and therapy of kwashiorkor in his doctoral thesis in Guatemala. He too considered it a multiple deficiency disease, but stressed the importance of protein deficiency as a contributory factor. Peña Chavarría *et al.*, in 1948,²¹⁰ were the first to call attention to its tremendous public health importance as a cause of death in young children. Peña Chavarría is also the originator of the term "flag sign" to denote the band of discoloured hair which becomes obvious by contrast as a child recovers from kwashiorkor.

Meneghello²¹¹ published the first extensive monograph on kwashiorkor in 1949 in Chile. This work emphasized the lack of adequate protein intake as the main cause of the disease, and discussed the effects of environmental conditions and intercurrent infections. In addition to a complete description of the clinical aspects and treatment of kwashiorkor, this monograph contains a bibliography of 35 other papers referring to the syndrome from Latin America and 27 articles from other parts of the world.

After 1950 the Latin-American literature on kwashiorkor increased very rapidly and reports appeared in almost every country. Initially this led to much confusion in terminology, as well as in treatment and preventive measures. However, the four conferences on nutritional problems in Latin America⁶⁻⁹ have done much to unify criteria, and the definition given by the third conference in 1954⁸ has been generally accepted. It is noteworthy that it is essentially the same as that of the third joint FAO-WHO Expert Committee on Nutrition which met in Africa in 1954.

The first clear affirmation of the similarity between kwashiorkor in Africa and Latin America was given in the 1954 monograph of Autret and Béhar¹²⁸ on kwashiorkor in Central America. Besides reviewing the Latin-American literature on the subject, they emphasized the frequency of kwashiorkor in Central America, and went into a detailed account of public health measures for its prevention.

This report was followed later by the studies of Waterlow and Vergara¹⁶⁸ on its occurrence and prevention in Brazil. These authors called attention not only to the similarities between kwashiorkor in Brazil, Africa and Central America, but also to the earlier age distribution in Brazil where most cases occur under 2 years of age; in Central America, they are more common over 2 years of age.

Clinical reports of cases of kwashiorkor have been published from

all the Latin-American countries.⁸ Two epidemiological studies have been completed in Venezuela. Bengoa *et al.*, in 1953,²¹² analysed vital statistics on deaths from deficiency diseases from 1940–1949, and concluded that deficiency diseases were responsible for more deaths in the 1–4 year age group than either whooping cough, diphtheria, measles or tuberculosis. “Avitaminosis”, rickets and pellagra were cited as the most frequently reported causes. It was stated that 5 per cent of all deaths in this group are probably due to kwashiorkor. Tovar-Escobar and Majo,²¹³ in 1955, described kwashiorkor as frequent among slum dwellers in Caracas.

The most extensive experimental work on kwashiorkor in Latin America has been concentrated in the “Hospital Infantil” in Mexico, and at the Institute of Nutrition of Central America and Panama (INCAP). Long series of reports on various aspects have appeared from each of these two institutions.

The Mexican investigators have had special interest in the electrolyte disturbances in kwashiorkor. They have found that the predominant alterations in electrolyte and water metabolism consist in an accumulation of water in the intracellular space accompanied by hypertonicity due to a marked loss of intracellular potassium.^{214–216} They have also reported a shift of sodium from the extracellular to the intracellular compartment.²¹⁷ In addition, these investigators have reported lowered plasma amino acid concentrations with a marked reversal in the tyrosine-phenylalanine ratio which they attribute to a decreased activity of tyrosine oxidase.^{218, 219}

Federico Gómez, Director of the “Hospital Infantil” in Mexico, and his co-workers, began comparisons of the use of soya protein and milk as early as 1949, and followed them with studies on nitrogen metabolism in children recovering from “third-degree malnutrition” (kwashiorkor), receiving tortilla diets supplemented with beans,^{220, 221} milk solids^{220, 222} and fish flour.²²³ By “third-degree malnutrition”,²²⁴ they refer to children over 40 per cent underweight whether with oedema (kwashiorkor) or without oedema (marasmus). Children with a weight deficiency of 26 to 40 per cent are classified as having “second-degree malnutrition”, while those with a deficiency of 10 to 25 per cent are classified as having “first-degree malnutrition”. In addition to extensive clinical descriptions,^{224–227} this group has also emphasized the frequency with which death in kwashiorkor is due to infection.^{228, 229}

Following the Autret and Béhar report in 1954,¹²⁸ INCAP began a systematic study of the epidemiology of kwashiorkor in Central America. The peak occurrence in children 2 to 3 years of age was

confirmed, as well as an underlying period of protein malnutrition referred to as pre-kwashiorkor,²³⁰ which occurs in all children of lower socio-economic groups in the area. The major importance of diarrhoeal disease and other infections in precipitating acute kwashiorkor was pointed out,³ and pathologically the frequency with which secondary infections are responsible for the death of children developing the syndrome was described.²³¹ Biochemical studies were made of the value of determinations of serum protein, amylase and pseudocholinesterase as measures of severity and rate of recovery from kwashiorkor,²³⁰ as well as of the low levels of xanthine oxidase and d-amino-acid oxidase activities which characterize the acute stage.²³² Another finding has been the impaired absorption and serum transport of vitamin A in kwashiorkor even when the dietary intake and liver stores appear adequate,^{233, 234} Most recent biochemical work demonstrates a relative insufficiency of adrenocortical hormones in kwashiorkor as contrasted with marasmus.²³⁵

In recent years the greatest attention has been given to the development of a low-cost vegetable mixture for the prevention of kwashiorkor.^{236, 237} INCAP Vegetable Mixture No. 9, consisting of 38 per cent cotton-seed flour, 29 per cent corn flour, 29 per cent sorghum flour, 3 per cent *Torula* yeast, 1 per cent CaCO_3 and 4,500 I.U./100 g. of vitamin A, contains 27.5 per cent protein of a quality similar to good animal protein. Under the name of "Incaparina", it is now successfully produced and employed in Central America for this purpose.

Other Deficiencies

During the last 10 years, reports of nutritional deficiencies in Latin America, other than those already covered, are relatively few. Cabezas,²³⁸ in El Salvador, found only 4 cases of rickets in a survey of 1,000 children. However, rickets is common in the city of Montevideo, according to Negro and Gentile Ramos.²³⁹ A few cases of this disease have been observed by Wiederhold and González²⁴⁰ in Venezuela.

Apart from mention in general nutritional surveys, no reports of the occurrence of scurvy and beri-beri have appeared. Pellagra has not been reported from Mexico in recent years, and the confusion of "infantile pellagra" with kwashiorkor in Yucatán has already been discussed.²⁰³

Paez Pumar *et al.*,¹¹¹ in Venezuela, and Gandra,²⁴¹ in Sao Paulo, Brazil, have emphasized the frequent occurrence of anaemia of nutritional origin especially in connection with repeated pregnancies and hookworm disease.

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CHAPTER 22

BACTERIAL SYMBIOSIS IN THE GASTROINTESTINAL TRACT

by

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MAN and animals live in symbiosis with microbes; in particular, the intestinal flora may act as a modifying environmental factor, and as such may influence growth, development and the metabolic processes of the host organism. It was Escherich^{1, 2} and his followers³⁻⁵ who first established the fact that the composition of the intestinal flora is primarily influenced by the food ingested and, in final analysis, by the milieu in the intestinal lumen acting as culture medium with selective capacity for bacterial inhabitants of the intestine.

The most impressive illustration for the causal relationship between food and intestinal flora is offered by infants fed either human milk or cow's milk formulæ. In contrast to the acid reaction of the fæces of normal breast-fed infants, the pH of the fæces of those infants given the usual cow's milk formulæ fall in the neutral or alkaline range. Unlike the mixed intestinal flora of infants on cow's milk formulæ, the intestinal flora of healthy breast-fed infants is characterized by the prevalence of a particular subspecies of *Lactobacillus*, i.e. *bifidus*. A Gram-stained fæcal smear obtained from healthy breast-fed infants appears to be almost uniform as if it would represent a pure culture of Gram-positive rods, characteristic of *L. bifidus*. On the average, the proportion of Gram-positive rods is around 98 per cent, with only slight variation in normal breast-fed infants.

This unexpectedly uniform fæcal flora in normal breast-fed infants has long attracted the attention of pædiatricians as a peculiar and specific characteristic of the healthy breast-fed infant. It has often been linked with the nutritional state, and the generally higher resistance of the breast-fed infant when compared with infants fed cow's milk.⁶⁻⁸

The question arises: In what respect is the chemical composition of human milk responsible for the specific intestinal flora in the breast-fed infant? In reviewing the chemical differences between

human and cow's milk, as they were known in the past, they are, although in several respects significant even when most pronounced, within the same order of magnitude. The relatively high ratio lactose : protein in human milk has been singled out in the past as perhaps the most important factor in determining the bifidus flora in the breast-fed infant.⁹ Lactose, the physiologic sugar of milk, is not easily split by enzymatic action in the intestine and its unabsorbed portion may promote fermentation, the production of acids and the propagation of aciduric *Lactobacilli* in the large intestine. In further consequence, lactose improves absorption and utilization of calcium.⁹

For most lactobacilli, in particular for *L. bifidus*, lactose is the preferred source of carbohydrate. On the other hand, free unsaturated fatty acids and fats containing C₁₂-C₁₄ saturated fatty acids may exert an inhibiting effect on *L. bifidus*.¹⁰ A cow's milk formula with low protein and high lactose content, and with adequate fat, should be conducive to the development of the *L. bifidus* flora, in analogy to the effect of human milk. However, in infants fed such mixtures, the predominant and uniform *L. bifidus* flora has never been observed, and the proportion of Gram-positive, bifidus-like rods seldom reached even 70 per cent.¹¹ Nevertheless, in infants fed such mixtures, the pH of the faeces reaches levels close to the acid pH found in breast-fed infants. Further, such mixtures promote the utilization of nitrogen, at least in comparison to formulæ in which the carbohydrate supplement was dextrimaltose instead of lactose. Infants fed such mixtures with dextrimaltose have shown also higher urinary phenol excretion than infants fed the lactose-containing formula.¹² These differences may be attributed to the varying effect of carbohydrates used on the composition and indirect metabolic effect of the intestinal flora. In animals the metabolic effect of various carbohydrates has often been considered, in the past, as secondary to their modifying effect on the intestinal flora.¹³

The unique effect of human milk in the production of the intestinal bifidus flora, not fully explained by the low-ratio protein : lactose in human milk, made it likely that human milk may contain a specific bifidus factor which should specifically promote the growth of *L. bifidus*.¹⁴

By the use of a variant of *L. bifidus*,¹⁵ the growth-promoting effect of human milk on this strain of *L. bifidus* indicated the presence of a specific microbiologically-active constituent(s). In contrast, cow's milk was practically inactive. Chemically, this "bifidus factor" belongs to the group of N-containing carbohydrates. As it occurs in human milk, it is not a uniform, well-characterized substance and is

present in low and high molecular compounds. Its most characteristic constituent in all these compounds is N-acetyl-D-glucosamine, an amino-sugar. In the higher molecular compounds N-acetyl-D-glucosamine is bound to galactose, glucose (or one could say, lactose), fucose and acetyl-neuraminic acid. The undialysable high molecular compound may be characterized as a mucopolysaccharide.¹⁵⁻²⁰

Streptogenin-like constituents of both human and cow's milk²¹⁻²³ may act as supplementary growth-promoting factors for *L. bifidus*.

The nutritional role of the bifidus factor(s), and in further consequence, that of the *L. bifidus* flora, in the physiology of the breast-fed infant is still shrouded in mystery. It is hoped that the avenue which was opened up by the recognition of hitherto unknown N-containing microbiologically-active carbohydrates and related compounds in milk, may lead to a better understanding of this still-open chapter in pædiatric nutrition.

It is of interest, and still unexplained, that the normal, uniform bifidus flora in the breast-fed infant establishes itself, especially in prematures, only after a period of several weeks and that the bifidus flora may change, in spite of continued breast-feeding, with impending parenteral infection.

The bifidus flora of the normal breast-fed infant is the pre-eminent example of a fermentative, saccharolytic, aciduric intestinal flora. The mixed flora of infants fed cow's milk, as well as the intestinal flora in all other ages, is characterized by a multitude of various fermentative and putrefying aerobic and anaerobic bacterial strains, with the prevalence of putrefaction. But even in such mixed intestinal flora exposed to changes in their intestinal medium as furnished by the great variability of food constituents and other environmental factors (infection, climate), there must exist a definite ecological system with its self-steering, although at present, unexplainable interrelationships. In this connection, mention should be made of fluctuations in the coliform population of the human intestinal flora. Recent studies²⁴⁻²⁷ revealed that *E. coli* appears to be represented in the intestinal flora as resident strains, that persist over relatively long periods of time, and of transient strains that remain for a much shorter period. Even a resident strain may disappear in time to be replaced by another resident strain. In general, it is practically impossible to implant foreign strains of *E. coli*, even by using enteric-coated capsules or after reducing the population of the bowel by chemical means. It was shown that even a strain which had been a "resident" for more than a year and then had disappeared, could not be implanted.²⁸ The mechanism of such definite pattern is

not clear, nor is the reason why a resident strain eventually is replaced by another strain. Among the theories suggested to explain this phenomenon are the possibilities that a bacteriophage might eliminate the resident strain, that diarrhoeic attack might alter the intestinal conditions, and finally, that one *E. coli* could produce antagonistic substances against other *E. coli*.²⁸ However, none of these three explanations has received support by evidence. On the other hand, it is conceivable that nutritional factors, as such, might interfere in this particular selection of resident strains which, in turn, might exert a secondary effect on the metabolism and thus on the nutritional state of the host organism.

On the nutrition and metabolism of the host organism, the intestinal flora may exert its effect in different directions: (a) Beneficially, such as through synthesis of essential nutrients (mainly of micro-nutrients) or through transformation of indigestible food constituents, for example, cellulose and other polysaccharides, especially in ruminants; (b) in a more harmful direction, as by utilizing nutrients and thus withholding them from the host organism, or by the formation of toxic metabolites, which adsorbed, may adversely affect the host organism; (c) adsorption of bacterial products which might act as antigens, could initiate and condition immunological reactions. These could be considered partly beneficial in so far as they promote preventive immunological response, or detrimental when they promote reaction of sensitization.

Intestinal flora as a possible source of vitamins, synthesized by bacteria, was first discussed by Cooper as early as 1914.²⁹ The first most-convincing proof for the synthesizing ability of the intestinal flora for a vitamin in man was furnished by the study of prothrombin-levels as an index of vitamin-K activity in the newborn infant.³⁰ Prothrombin-levels in the serum, after an initial drop following delivery, show a sudden increase after the first 3 to 5 days of life, apparently synchronized with the establishment of a bacterial flora in the intestine.

There exists a wide literature on the synthesis of vitamins by the intestinal flora in experimental animals. It is outside the scope of this presentation to review the extensive experimental material, in detail. It should suffice to call attention to a few basic observations gained by experiments in animals. Fridericia³¹ described spontaneous recovery in rats kept on a diet-deficient in the vitamin B complex, without the addition of vitamin-containing supplements. The exact nature of this phenomenon, called refection, is not yet determined. It is still an open question whether it is due to intestinal absorption

of vitamins synthesized by the bacteria, or to coprophagy. The best and unequivocal evidence, not only for the role of intestinal bacterial synthesis of vitamins, but also for other nutritional efficacy, was first furnished by experiments on rats, and later on other animal species fed purified diets supplemented with various sulphonamides.³²⁻³⁵ In addition to vitamin K, biotin, folic acid and, to some extent perhaps nicotinic acid, may be furnished by intestinal bacteria and their intestinal synthesis may be suppressed by sulphonamides. Experiments with sulphonamides on human volunteers³⁶⁻³⁹ seemed to indicate that such synthesis of various vitamins or vitamin-like compounds may occur also in man through metabolic activity of the intestinal flora. However, these observations were largely inconclusive with regard to the availability of these bacterial products for the host organism.

The first observation of the beneficial effect of antibacterial substances for the nutritional state of animals was reported by Moore and co-workers in 1946.⁴⁰ They found that succinylsulphathiazole and streptomycin increased the growth of chicks on a purified diet.

Greater and general interest in antibiotics, as useful dietary supplements, in practical animal husbandry was stimulated and spread widely only since 1950, through the studies of Jukes and his associates on the growth-promoting effect of antibiotics in animals.⁴¹ At present, antibiotics such as penicillin, the tetracyclin group, and others are widely-used as supplements in commercial animal feeds. A very extensive literature on antibiotics as growth-stimulants and dietary adjuvants has accumulated during the past 10 years.^{41, 42} Nevertheless, the mechanism by which the antibiotics produce their effects on nutrition is still an open problem. It is generally related to the action of antibiotics on the intestinal bacteria. "When antibiotics are administered, the total numbers of bacteria in samples of the intestinal contents characteristically decrease for a few days and then increase above the original levels. Perhaps, antibiotics suppress certain bacterial forms which are inhibitory not only to the growth of the host, but also to the growth of some of the other intestinal bacteria."⁴¹

Seen from this angle, it is not surprising that observations on the nutritional effect of antibiotics vary widely, not only in different laboratories, but often, in the same laboratory at various times. It has been claimed that the intestinal flora may show equal variations. Growth-promotion by antibiotics would then occur only when bacteria are present in the gut, which, in themselves retard growth

of the host and may be eliminated under the influence of antibiotics.^{41, 42} It was in accord with this assumption that the growth-promoting effect of antibiotics was found to disappear or be diminished when chicks were raised in clean quarters.⁴³ In addition, the promotion of growth in animals under the influence of particular antibiotics may be related to the relief of subclinical or clinically-mild intestinal infections. *Clostridium* has been widely named⁴² as the bacterial species around which the growth-promoting effect may be centred. A particular strain of *Clostridium* was isolated in the National Institute for Research in Dairying in Reading (England) which was found to be present in chicks which responded with enhanced growth to the administration of antibiotics and was found to be absent in refractory animals.⁴⁴

Difficulties of proper controls have made studies in the growth-promoting of antibiotics in infants and children even less easy to assess than those carried out on animals. The most impressive, positive results were reported by Scrimshaw and his associates^{45, 46} on Mayan children 7-12 years of age, living in the Guatemalan highlands and subsisting on diets low in animal protein. Chlortetracycline exerted a pronounced effect on growth. This effect was observed in the spring months and was related to the suppression of seasonal infections in the children. The response to penicillin was variable and not as consistent as with tetracycline.

Antibiotics may exert their effect on the intestinal flora either through elimination of toxic factors or by sparing beneficial nutrients. Suppression of infection is considered in this context as tantamount to elimination of toxic factors. The sparing effect of antibiotics as mechanism of their action is apparently rarely—if at all—encountered in man. More conclusive evidence for the harmful role of toxic metabolites produced by clinical observations on patients with severe liver disease, near decompensation. Sherlock and her associates have found⁴⁷ that in such patients, toxic substances might be derived from methionine by the action of intestinal bacteria. In a group of 9 patients with portal cirrhosis and chronic portal systemic encephalopathy, of whom 8 had extensive portal systemic collateral circulation, dl-methionine given daily in the excessive dose of 8 to 20 g. for up to 7 days, neurological deterioration was noticed in 7. Intravenous methionine was without effect in 3 of 4 patients who reacted to methionine by mouth; in the fourth, deterioration occurred 2 hours after the infusion. Neurological signs after methionine by mouth were not associated with change in blood-ammonia, pH or serum bilirubin nor related to the level of

methionine which rose whether there was neurological deterioration or not. Five patients who responded with deterioration of the neurological condition (pre-coma) to methionine by mouth were given chlortetracycline before and during a second course of methionine. In accordance with the assumption that the toxicity of methionine given in such excessive large doses to patients with liver disease in state of decompensation is due to breakdown products caused by intestinal bacterial action, chlortetracycline prevented or delayed toxic clinical manifestations.

Such toxic substances are normally formed in the intestine from nitrogenous food constituents in varying quantity. The normal liver may metabolize or detoxify them. In case of decompensated liver or through bypass due to collaterals, such products (ammonia and related substances) may exert toxicity of varying degrees in several organs, particularly in the brain, and are thus the major cause of hepatic coma. In this connection, the most consistent finding in hepatic coma is the increased ammonia-content in the blood.⁴⁸⁻⁵²

Such increase in the values of serum ammonia may also follow the intravenous injection of urea. Since administration of antibiotics by mouth prevents such increase, it was postulated⁵³ that part of intravenously injected urea is excreted into the lumen of the intestinal tract (through the bile) and, there exposed to the effect urease of intestinal bacteria becomes the source of ammonia. Suppression of such bacterial action should protect the urea and should prevent the formation of absorbable ammonia.

Reduction of protein intake, in some instances, to a drastically low level (25 g. per day) may improve neurological manifestations characteristic of the so-called "portosystemic encephalopathy",⁵¹ seen in patients with cirrhosis and abnormal communications between the portal and systemic circulations. Toxic products may also originate from the bacterial decompensation of intestinal secretions or cell-debris. Both reduction of protein-intake and oral administration of appropriate antibiotics are now generally used in the management of hepatic coma or threatening hepatic decompensation.^{51, 54, 55} Since the bacteria often become refractory to the antibiotics used, coma may reappear during treatment if the hepatic condition has not improved sufficiently in the interim. This may explain the transient, and by no means regular, effect of antimicrobial agents in improving hepatic coma.

The sparing effect of antibiotics concerning a beneficial nutrient was well-demonstrated in animal experiments in which antibiotics such as chlortetracycline and penicillin were used to delay the

development of experimental dietary necrosis of the liver.⁵⁶ In this set of experiments, penicillin and chlortetracycline have delayed the development of fatal hepatic necrosis only when they were administered during the whole duration of the experiment. No significant beneficial effect was noticed when the administration of the antibiotics was begun after the rats were kept for about 4 weeks on the unsupplemented basal experimental diet. These observations are in closest accord with the hypothesis that necrosis develops after the experimental animals have become depleted of protective food constituents. Antibiotics appear to prolong this period of depletion.

An impressive illustration of the sparing of a nutrient through the action of antibiotics in man is furnished by the effect of antibiotics on the metabolism of choline. When a relatively large amount of choline is ingested by normal persons, about 60 per cent appears in the urine as total trimethylamine mostly within 24 hours.⁵⁷ Oral administration of chlortetracycline, oxytetracycline and penicillin or sulphaphthalidine, but not intravenous chlortetracycline, causes a considerable reduction in the urinary excretion of trimethylamine after simultaneous ingestion of a test dose of choline, as the result of a diminished intestinal degradation of choline to trimethylamine by intestinal bacteria. With continuous administration of antibiotics, such as penicillin, the antimicrobial effect disappears within 1 or 2 weeks, indicating a refractory state of the bacteria.⁵⁸ Thus, in this particular case, antibiotics may help, at least temporarily, to increase the available amount of ingested vitamin by protecting it from bacterial degradation in the intestine. Such sparing of a vitamin could easily be mistaken for its intestinal synthesis under the influence of the antimicrobial agent in question.

Sparing of intestinal destruction of vitamins must be the explanation for the beneficial effect of some antibiotics in rats fed rations deficient in B vitamins, such as pyridoxine or riboflavin or pantothenic acid. This positive effect of antibiotics observed by Daft and his associates,^{59, 60} is not seen in all the animals treated, but on the other hand, if present, it may last for many months.

Antibiotics may also produce secondary metabolic effects which are not of strictly nutritional nature, and as such may not fall in the category of beneficial or harmful reactions. In our laboratory, it has been found that rats fed a diet producing necrosis of the liver, or the same ration, supplemented with cystine or vitamin E, excreted large amounts of ether soluble acids, especially methylmalonic acid in their urine. Rats on the same diet supplemented with chlortetracycline and penicillin, excreted only small amounts of these acids. This

effect persisted as long as the antibiotics were given and is the first long-term *in vivo* effect noted of chlortetracycline and penicillin.⁶¹ The urinary excretion of methylmalonic acid was increased in rats fed the necrogenic basal ration after supplementation with valine. This increase after administration of valine was not observed in rats which were kept on the necrogenic diet and received supplements of chlortetracycline. In contrast, in liver perfusion experiments, the production of methylmalonic acid from valine (or from propionate) took place regardless of whether chlortetracycline was added to the perfusion mixture or not. These experiments seem to indicate that chlortetracycline acts through the bacterial flora of the intestine, and not primarily through the metabolism of the liver.⁶²

It has been claimed^{63, 64} that irreversible post-hæmorrhagic shock, as produced experimentally in animals, may be beneficially influenced by preventive medication with antibiotics. The further assumption has been made that antibiotics may eliminate intestinal bacteria which produce endotoxins of primary ætiologic importance in the chain of events leading to irreversible shock. Potentiation of bacterial endotoxins in the state of vascular collapse accompanying post-hæmorrhagic shock has also been advanced as a secondary causative factor. If any of these factors were instrumental in the production of irreversible post-hæmorrhagic shock, animals raised under germ-free conditions should be resistant to the same post-hæmorrhagic shock, which in conventional animals ends in fatal shock. This, however, was not the case. No distinct difference was observed in the behaviour of conventional and germ-free rats when they were exposed to the conditions of irreversible post-hæmorrhagic shock. Germ-free rats have developed shock of apparently the same intensity and in about the same time as the conventional controls.⁶⁵⁻⁶⁸ Whether the unavoidable, possible admixture of traces of endotoxin and bacterial bodies in the sterilized semi-synthetic ration fed to both groups may play a role in the production of shock under germ-free conditions, only further special studies will be able to decide. In this connection, it would be important to see whether the beneficial effect of some antibiotics on the prevention of irreversible post-hæmorrhagic shock may be duplicated in germ-free animals. That such chemically different antibiotics as the tetracyclines and neomycin might exercise a similar effect on the cardiovascular system entirely apart from their antibacterial activity seems *a priori* unlikely. McNulty, in the Germ-free Laboratory of the Walter Reed Army Institute of Research, Washington, D.C., U.S.A., found, in effect, no appreciable difference in appearance of post-hæmorrhagic

shock and mortality of germ-free rats with or without treatment with antibiotics.⁶⁸

Germ-free animals are uniquely qualified for the study of the symbiosis of intestinal bacteria with the host. The technique for the study of "germ-free life" even in higher vertebrates, has sufficiently advanced—from the pioneering work of Reyniers to the ingenious "remote-control" of Miyakawa—to carry out studies of various kinds on such animals.^{69, 70}

Rats were reared under "germ-free" conditions through ten or more generations. In general, germ-free chickens and turkey-poults have shown better growth than the conventional animal controls.^{71, 72} No indication was found for the existence of hitherto unknown essential dietary factors, which might be furnished in conventional animals by the intestinal bacteria. Unexplained, is the greatly enlarged cecum and adjoining large intestine in germ-free animals.⁷³

The role of intestinal bacteria in the general immunological response of the host-organism is of special interest and importance. The lack of—or greatly reduced—gammaglobulin fraction, and the increased serum-albumin content may be best linked to the absence of antigenic stimuli and a compensatory mechanism in the germ-free animal.⁷⁴ The delayed appearance of some antibacterial agglutinins⁷⁵ and anti-human blood group B agglutinins^{76, 77} may be traceable to the bacterial contamination of the diet prior to autoclaving. Oral mono-contamination with live *E. coli* 086 will increase promptly the titre of antihuman blood group B agglutinins in originally germ-free Leghorn chicks.^{76, 77} The coating of red blood cells with a substance of blood group B activity reported recently^{78, 79} in man, must be due to the absorption of blood group B-like substances of bacterial origin from the intestine. Such temporary coating of red blood cells with a substance exhibiting B-group activity may be effected by feeding infants suffering from acute intestinal upset with dead *E. coli* exhibiting high blood group B activity.⁸⁰ In these and similar observations, we are dealing with the influence of intestinal bacteria and their products on immunological phenomena. It is certain that the germ-free animal will prove to be a very valuable tool for the study of immunological reactions, including the all-important problem of specific and natural resistance.

There is general agreement^{68, 71, 72, 81} that antibiotics have no effect on the growth of germ-free animals. Specifically, experiments with penicillin in chicks, and with penicillin and oleandomycin on turkey-poults, confirmed the premise that these antibiotics act as growth-promoters through the intestinal flora, apparently—as

shown on mono-contaminated birds—chiefly through the reversal of growth-depression caused by *Cl. welchii*. The fact that in the presence of other bacteria such as *E. coli*, *L. lactis* and *S. liquefaciens*, the depression of growth caused in chicks by *Cl. welchii* was not fully restored is a point which requires further elucidation. The generally higher growth-rate of germ-free chicks compared with conventional controls without or with treatment of penicillin seems to indicate that there must be other factors, probably in the form of penicillin-resistant intestinal bacteria which contribute to the depressed growth of the conventional chicks. The higher growth-rate of germ-free chicks is due to greater food consumption and not to better food efficiency.

Germ-free animals offer excellent opportunities for the study of many metabolic reactions in which intestinal bacteria, under conventional conditions, may play a more or less decisive role. Comparison of such reactions using conventional and germ-free animals should add to our knowledge of the basic symbiotic processes in the interaction between intestinal bacteria and host organism. Illustrative examples may be found in the series of investigations of Gustafsson and his associates. They have confirmed through unequivocal experimental evidence, the generally-held assumption that vitamins may be synthesized and furnished by intestinal bacteria. The same autoclaved ration, free from vitamin K, which in conventional rats prevented vitamin K deficiency, promoted fatal hæmorrhage in germ-free rats.⁷³ Since these experiments were done on rats, it should be borne in mind that the preceding observations on the bacterial synthesis were made on animals in which coprophagy could not have been categorically excluded as a complicating factor. With a very ingenious technique Barnes *et al.* have shown that the nutritional behaviour of animals in which coprophagy was strictly prevented may significantly differ from animals on the same diet, while kept under the usual experimental conditions (in single cages) but still with access to their fæces.^{83, 89} Specifically, rats on a vitamin K-free ration will not develop vitamin K deficiency but rats on the same ration, and, prevented from eating their fæces, will have shown uniformly severe vitamin K deficiency. This indicates that vitamin K synthesized by bacteria is not absorbed from the large intestine, but becomes effective only after ingestion. Similar observations were made also regarding deficiency of vitamin B₁₂⁹⁵ and essential fatty acids.⁸⁸ The significance of these findings in relation to human nutrition requires further exploration. With regard to the present discussion on the part which cholesterol, and possibly bile acids, play

in the pathogenesis of arteriosclerosis, it is of interest to note that on a standard diet with no cholesterol added, germ-free rats had significantly higher serum cholesterol values than the control rats⁹⁰ and the half-life of cholic acid in germ-frees was found to be 11.4 days as compared with 2 days in control animals. When the rat was taken out of the germ-free apparatus, turnover time and bile acid degradation changed to that of conventional animals. The delayed turnover of cholesterol and bile acids must have a considerable effect on interrelated, although perhaps only secondarily connected metabolic processes.

It is not surprising that no indicane, stercobiline or urobiline was found in the urine or faeces of germ-free rats.⁷³

This short enumeration of only a few available data obtained by the study of germ-free animals should serve as illustration that this avenue, which by technical progress and modern nutritional knowledge only recently became wide-open, is worthy of intensive exploration.

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CHAPTER 23

PROTEIN MALNUTRITION AND ITS PREVENTION AND TREATMENT WITH SPECIAL REFERENCE TO KWASHIORKOR AND MARASMUS

by

J. D. L. HANSEN

THE great importance of proteins in nutrition has, in the last decade, become much more generally appreciated by clinicians and public health administrators than at any previous time. This is mainly because of the interest that has arisen in the widely prevalent syndromes of protein deficiency in children known as kwashiorkor and marasmus. Research into the pathogenesis of these syndromes has led investigators into a study and clarification of many aspects of nutritional physiology that are of practical value with regard to the protein requirements of individuals and of population groups.

THE CLINICAL SYNDROMES OF PROTEIN DEFICIENCY IN CHILDREN—KWASHIORKOR AND MARASMUS

Kwashiorkor. The word "kwashiorkor" was used by the Ga tribe of Accra, the capital of the Gold Coast (now Ghana) for the sickness of the weanling child. The term translated literally means first-second, and refers to the child as deposed, i.e. deposed from the breast when the next baby is born, or when the mother again becomes pregnant.⁴⁶ Cicely Williams, in 1933, gave a clinical description of the disease when she worked on the Gold Coast, and applied the local native name, kwashiorkor, to it.^{52, 53} The children that she described all had a history of an abnormal diet. They had been weaned on to maize gruels, low in protein content, and within 3–4 months began to sicken. Brock and Autret firmly established the name kwashiorkor for the syndrome in Africa, and its relationship to a low-protein diet.⁵ Kwashiorkor is at present the most popular term but the syndrome has been described in the literature under many different names, of which the following are among the best known: malignant malnutrition, infantile pellagra, fatty liver disease, nutritional oedema, Mehl-nährschaden, wet marasmus, infantile

œdema, nutritional dystrophy, syndrome policarencial infantil, third-degree malnutrition and, more recently, protein calorie malnutrition.²⁵

Kwashiorkor characteristically occurs amongst weanling children aged 1–4 years whose diets are habitually poor in protein, while they are more nearly adequate in calories. No age is, however, immune, for infantile, juvenile and even adult varieties have been described.⁴⁶ The syndrome is found all over the tropical belt of the world but extends well outside the tropics into both northern and southern hemispheres. It is found amongst underprivileged sections of populations, particularly those who subsist mainly on cereal staple foods such as maize, rice, cassava and wheat and amongst whom the consumption of animal protein foods such as meat, fish, milk and egg is very low. It is also seen amongst children of broken homes and poor urban conditions where poverty, lack of care, and/or ignorance prevent the purchase of milk and animal products for post-weaning feeding. Full descriptions of the syndrome with all its manifestations and variations may be found elsewhere.^{2, 5, 25, 36, 39, 46}

In its classical form kwashiorkor has the following main clinical features:

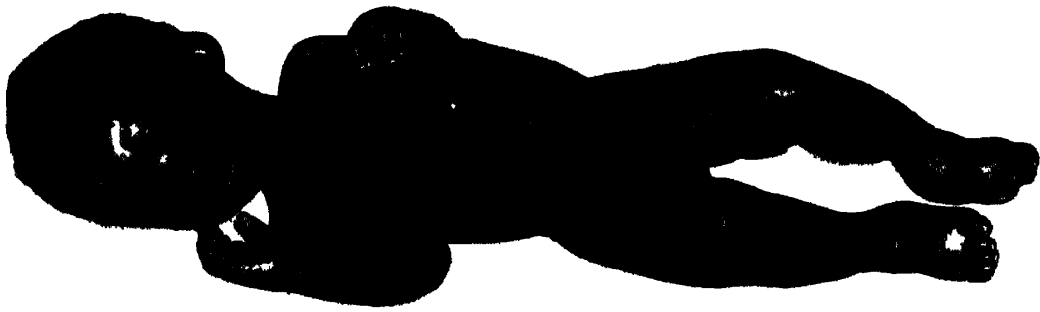
(a) *Growth Failure*. This is always present and is manifested by a low body weight for age and decreased length. The co-existence of œdema and in some cases of excess subcutaneous fat gives a deceptive appearance. The skeletal muscles are weak, thin and atrophic.

(b) *Mental changes* in the form of irritability and apathy.

(c) *œdema*. This is always present and may be minimal, affecting the feet only, or gross, involving the whole body including the face. Ascites and pleural effusions are unusual. Some children have the appearance of dehydration and wasting in the upper half of the body and œdema in the lower half.

(d) *Dermatoses*. These include pigmentation, depigmentation, desquamation and ulceration. The characteristic distribution is on the lower limbs, buttocks and perineal areas but any part of the body may be involved. This is in contrast to pellagra where similar lesions occur mainly on exposed surfaces. The presence of the characteristic rash is not necessary for the diagnosis of kwashiorkor, but when present it is pathognomonic.

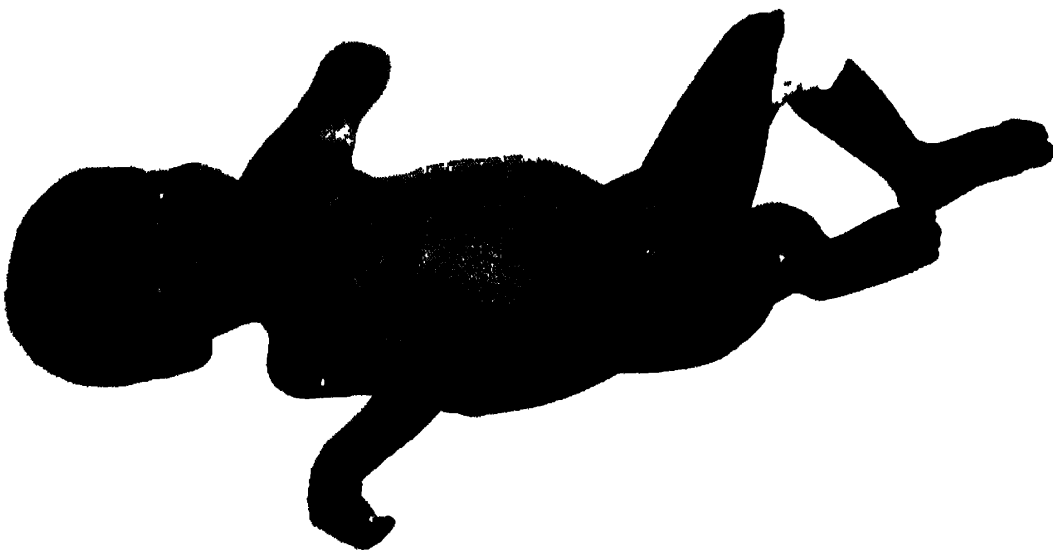
(e) *Hair Changes*. The hair is often sparse and thin and loses its elasticity particularly over the temple regions. In dark-haired individuals there is often dyspigmentation with development of a streaky red or grey colour.



A



B



C

FIG. 1.

- A. Marasmic kwashiorkor Age 21 months, with skin lesions and edema. Weight 7.5 kg
- B. The same case after diuresis Weight 6.7 kg
- C. Marasmus Age 22 months Weight 6.6 kg No skin lesions No edema

Note the similarity between B and C.

[To face page 26]

(f) *Gastro-intestinal Symptoms.* Anorexia and vomiting are common and diarrhoea, with large bulky stools, is usual.

(g) *Anæmia.* This is commonly but not invariably present and may be normocytic, macrocytic or hypochromic. Its ætiology varies with locality and depends on the availability of hæmatinic factors such as iron, folic acid and vitamin B₁₂ in the diet.

Marasmus. This is a term applied to infants who are grossly underweight and have atrophy of both muscles and subcutaneous fat. There is a shrunken, wizened appearance of the face in contrast to fat rounded cheeks of kwashiorkor. There are usually no hair or skin changes and œdema is unusual and always minimal (see Fig. 1). As in kwashiorkor, diarrhoea is common. Apart from nutritional causes the same clinical state may be produced by a number of conditions including tuberculosis, congenital syphilis and gastro-enteritis as well as various rare metabolic disorders. Dietary marasmus is, however, by far the most common ætiological variety.

There are many intermediate clinical states between marasmus and kwashiorkor and many borderline cases that defy accurate clinical classification. If the basic similarity between marasmus and kwashiorkor is recognized (see Fig. 1), the task of the clinician is made much easier. Both syndromes are associated with low-protein diets and manifest severe growth retardation. If calories from sugar or starchy foods have been plentiful, there may be a large amount of subcutaneous fat giving rise to the so-called "sugar-baby" type of kwashiorkor. Where in addition to protein deficiency there has been a severe calorie deficiency the syndrome of marasmus develops. Borderline cases are frequently known as marasmic kwashiorkor. There is now experimental evidence in animals that it is this factor of caloric intake that determines the difference between kwashiorkor and marasmus. In piglets on a low-protein diet a syndrome resembling marasmus can be produced. If the diet is supplemented by additional carbohydrate a condition resembling kwashiorkor develops.²²

It should be noted that specific vitamin, mineral and trace element deficiencies may add to the basic clinical picture in areas where these deficiencies occur.

The serum chemistry findings of diagnostic value in protein deficiency are as follows:

(a) *Serum Proteins.* Hypoalbuminæmia is at present the most specific biochemical abnormality. In kwashiorkor the hypoalbuminæmia may be severe though in marasmus it may not be so striking.

The mean values determined in two centres are as follows:

	<i>Kwashiorkor</i>	<i>Marasmus</i>
	(g. %)	(g. %)
Jamaica ²⁴	1.7	3.1
Mexico ¹⁰	1.64	2.59

The range of values for kwashiorkor in one hospitalized series is shown in Fig. 2.

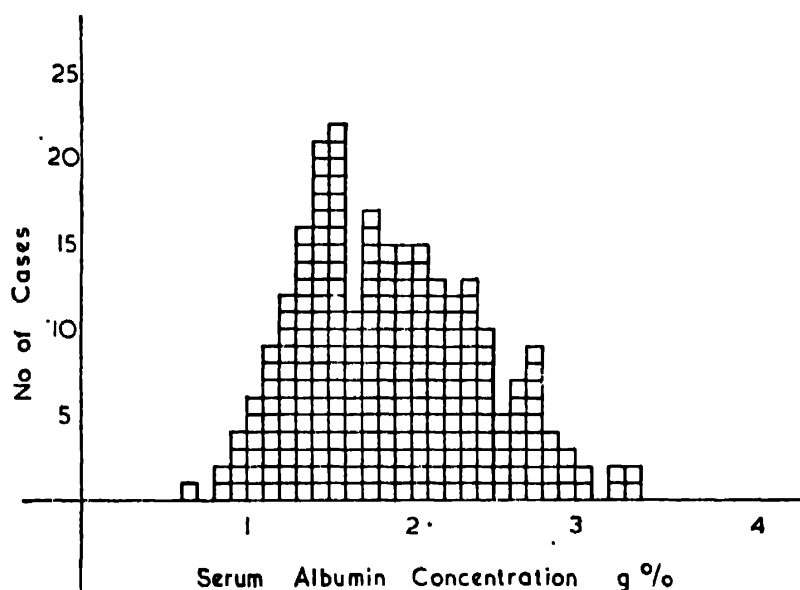


FIG. 2. The distribution of serum albumin concentration in 266 cases of kwashiorkor admitted to hospital.

The serum globulins may be raised, normal or lowered. The degree of depression of serum albumin is not always correlated with the clinical severity of the case nor with the degree of oedema.¹⁸ Rise of serum albumin is a good index of recovery and the rate of rise may be used to judge efficiency of therapy.⁶ Hypoalbuminæmia can be assumed to be a reflection of protein-depleted tissues due to the protein-deficient diet.¹ There is at present no evidence that there is an abnormality in the mechanism of albumin synthesis or breakdown. Experimentally in animals it has been shown that when serum albumin concentration begins to fall protein depletion is already of severe degree. The intravascular plasma albumin concentration is at first protected by a proportionately greater decrease of extravascular extracellular protein.⁵⁵

(b) *Serum and Liver Enzymes.* There is a lowering of serum enzyme activity in particular of serum amylase, esterase, cholin-

esterase, lipase, and alkaline phosphatase. Together with these there is diminished activity of lipase, amylase and trypsin in the duodenal and pancreatic secretions.⁵¹ In the liver D-amino acid oxidase and xanthine oxidase are low.⁷

(c) *Serum Electrolytes*. Serum levels of sodium and chloride are not necessarily altered and a wide range of values has been reported. Serum potassium is often depressed particularly in the acute phases of the disease in the presence of diarrhoea.^{18, 31}

(d) *Other Serum Constituents*. Diminished serum urea and cholesterol are always present.¹¹ Cholesterol rises rapidly within a few days of the onset of treatment.³⁵

Body Composition

Tissue analysis has confirmed the increase of total body water and of extracellular fluid in cases with and without oedema¹⁵ (see Ch. 20). During loss of oedema there is a sodium chloride diuresis and as much as a 10–20 per cent loss in body weight.¹⁸ There is a 25–30 per cent loss of body potassium as measured by balance¹⁸ or by isotope methods⁴² and body magnesium is probably also reduced.²⁹ At autopsy there is striking evidence of protein depletion in the form of wasted muscles and biopsies of muscle and liver during life have confirmed that these tissues are grossly depleted of nitrogen.^{49, 50} The liver is large, yellow and bloodless because of extensive fat infiltration. The acini of the pancreas are atrophic with loss of zymogen granules. The intestines are often distended and show atrophy of mucous membrane and muscle coats.⁴⁶

Sub-Clinical Protein Deficiency in Children—Pre-Kwashiorkor

It has in recent years become apparent that the full clinical syndromes of marasmus and kwashiorkor are only part of the problem of protein malnutrition.³⁹ Several authors have pointed out that the death rate in the age group 1–4 years is a much better index of malnutrition and poor conditions than the orthodox infantile mortality rate. It has been stated that, roughly, the toddler (1–4 years) death rate corresponds with the nutritional state of the region gained from personal surveys and the literature.⁵⁴ Countries in which kwashiorkor is found are those which have exceptionally high pre-school mortality rates.^{33, 39} Vital statistics in these areas reveal excessive mortality rates from gastroenteritis, pneumonia and other infections such as meningitis and primary tuberculosis.

Many practitioners during the process of death certification do not note that these children are also malnourished and give the terminal disease as cause of death. With modern forms of therapy, death should not occur from these diseases and in countries where nutrition is good the death rates are negligible. In England, for example, the death rate from gastroenteritis is 300 per year. In South Africa, with a non-white population that is quarter of the size of the total population of Britain, gastroenteritis deaths amount to 11,000 in the towns alone.³³

Admittedly, in practice it is extremely difficult to disentangle the effects of malnutrition and infection but it should be understood that official mortality statistics are very misleading with regard to evidence of nutritional causes of death. The nutritional factor is frequently not taken into account unless there are very specific well-known signs of malnutrition present. Often the only evidence of malnutrition at death is that of low weight for age and no note is made of this on the certification form. It has been established that many of these children before contracting their terminal illness are well below normal weight for age.³³ Subclinical protein deficiency will show itself characteristically in the post-weaning phase by a falling-off of weight gain and a predisposition to diarrhoea and respiratory infections. This borderline malnutritional state has been called pre-kwashiorkor, or first-grade malnutrition, and one estimate is that for every case of kwashiorkor in a population group there are at least 100 cases of underlying protein malnutrition.³⁹ A good analogy is that kwashiorkor and marasmus represent two visible peaks of an iceberg. The submerged part of the iceberg would represent the sub-clinical form of protein deficiency.³⁹

Protein Deficiency in the Adult

Signs of protein deficiency in the adult are not so clear cut as in the child.⁴⁶ This is presumably because the demands of growth for protein are no longer present and the results of deficiency are not so obviously manifest. There is evidence that in areas where protein deficiency syndromes of children are endemic the adult population is also protein-deficient. For example, surveys of adult Africans show lower serum albumin concentrations than Europeans in the same area.²⁶ It has also been demonstrated that total exchangeable albumin was smaller in five "healthy" African adults than in whites.⁸ Body composition studies likewise revealed protein depletion among Africans in the tropics.²³

The Pathogenesis of Kwashiorkor

Kwashiorkor used to be regarded as a disease that was almost invariably fatal.^{5, 46} The use of skimmed milk in treatment, introduced in the late 1940s, considerably improved the prognosis. Although it was known that the syndrome was related to a low-protein diet the exact nature of the deficiency or deficiencies present was incompletely understood. Therapeutic trials with synthetic diets had established by 1956 that cure could be initiated with a mixture of synthetic amino-acids, glucose and minerals.¹⁹ The presence of vitamins in this synthetic diet improved the rate of cure but it was noteworthy that complete resolution of skin and mucous membrane lesions was possible even in the absence of vitamins. These investigations established that the main limiting nutrient in the diet of children who develop kwashiorkor is protein.^{6, 19} In different areas and circumstances super-added calorie, vitamin and other deficiencies, e.g. mineral and trace element deficiencies and infections, modify the basic clinical picture.

The role of infection in kwashiorkor is an interesting one (see also Ch. 29). A recent postulate is that one effect of an inadequate protein diet is a disturbance of intestinal flora and that this plays a significant part in the clinical picture of kwashiorkor.⁴³ A high proportion of cases dying in one series has been reported to have had positive blood cultures of intestinal organisms.⁴⁴ In a discussion of these findings, it is pointed out how closely similar is the response to infection of children with kwashiorkor to that seen in premature infants and neonates. This is further supported by an apparent susceptibility of cases of kwashiorkor to generalized herpes simplex infection—nearly all previous reported cases having been in the neonatal age group.²⁸

At present the most reasonable concept of the development of the full syndrome is that long-continued ingestion of low-protein (cereal or tuber) diets leads to a state of sub-clinical protein deficiency described best by the term pre-kwashiorkor. It can be recognized in subnormal growth and health. In endemic regions there are many of these children and some precipitating factor or stress such as diarrhoea, parenteral infection, maternal deprivation, or family disruption of any form, abrupt loss of income causing more acute protein lack, or excessive extremes of environmental temperature produces the full syndrome of protein deficiency.^{30, 33} The availability of calories likewise determines whether the protein-deficiency syndrome will be kwashiorkor or marasmus or some intermediate state.

Protein Requirements

Quantitative. The recognition of the wide prevalence of the syndromes of protein deficiency in underdeveloped countries has led to the revaluation of protein requirements for all age groups.¹⁴ In many areas increases of population have outstripped available supplies of milk and other animal protein products. Protein requirements in these countries have to be met from vegetable sources which are usually the cereal and tuber proteins such as maize, wheat, cassava, manioc and rice. In these foods the protein content is low (10 per cent or less of the dry product compared with 35 per cent in dried skimmed milk) so large amounts have to be eaten if quantitative requirements are to be met.

There has been much discussion as to what constitutes minimal protein requirement. A special committee set up by FAO of the United Nations has endeavoured to lay down minimum standards according to present knowledge.¹²⁶ These are summarized in Fig. 4, p. 47, and represent the minimum requirements of milk protein in the various age groups for healthy individuals. These figures would be inadequate in disease states or when proteins of lesser nutritive value are used. It should be noted that during periods of maximum growth such as early childhood and in adolescence protein requirements are higher. During pregnancy also there is an increased demand for protein which is estimated at 10 g. protein per day beyond that of the unencumbered adult. During lactation probably at least 20 g. of additional protein are required per day. Various pathological states may require increase in protein intake. This applies in particular where there is interference with absorption of protein from intestinal infections. During convalescence from various medical and surgical conditions increased protein intake is necessary to make good losses incurred at the time of the acute episode.

Qualitative. The work of Rose³⁴ established that for men as well as for animals there are eight so-called essential amino-acids which cannot be manufactured by the body and must be supplied by protein foods to enable tissue synthesis to take place. These amino-acids are isoleucine, leucine, lysine, phenylalanine, methionine, threonine, tryptophan and valine. The same eight essential amino-acids plus histidine are necessary for the growth of young infants.⁴⁵ The essential amino-acid requirements of adults and infants as they are now known are shown in Table 1.

The cereal proteins in particular and many other proteins of vegetable origin are known to be relatively lacking in one or other essential amino-acid. For example, maize is deficient in lysine,

TABLE 1

The Average Minimal Daily Amino-Acid Requirements of Humans

<i>Amino-Acid</i>	<i>Infants mg./kg.</i>	<i>Female</i>	<i>Adults Male mg./day</i>
Histidine . . .	32		
Isoleucine . . .	90	450	700
Leucine . . .	150	620	700
Lysine . . .	90	500	800
Phenylalanine . . .	90	220	1,100 (300 if tyrosine present)
Methionine . . .	65	350	200 (if cystine present)
Threonine . . .	60	305	500
Tryptophan . . .	22	157	250
Valine . . .	93	650	800

The amino-acid requirements for adults are expressed as mg. per day because of poor correlation with weight of individual. The table is adapted from recent reviews on the subject ^{9, 13, 45} from which original references may be obtained.

tryptophan and isoleucine and wheat in lysine.¹³ Populations consuming cereals as their main source of protein therefore have not only a low-protein intake but one that may predispose to specific amino-acid deficiency. Proteins of animal origin, on the other hand, are rich in essential amino-acids and are usually higher in protein content on a dry weight basis than vegetable proteins. Protein requirements therefore are very much dependent on the quality of a protein with respect to its amino-acid content.

The Problems of Prevention of Protein Deficiency

Because of their relatively high protein requirements in relation to size young children are the first to suffer from the effects of a general shortage of protein. During the period of breast or bottle feeding, protein requirements are usually (but not always) met. It is the post-weaning child or pre-school child that is particularly affected.^{39, 46, 52, 53} A common practice, dictated either by socio-economic factors or prevailing agricultural patterns, is to place these children on to low-protein cereal foods such as maize, cassava and rice, etc. As indicated above, these foods satisfy neither total protein nor essential amino-acid requirements. The main public health problem

to be faced is therefore either to increase the supply of animal protein products to affected populations or to encourage the use of alternative sources of proteins, such as fish or high-protein vegetable mixtures.^{13, 37}

In addition to the problem of supply, there is the equally perplexing one of inducing a change in popular feeding habits. This requires health educational campaigns on a large scale which in turn are dependent on the training of sufficient adequate personnel. The latter need, in addition to their normal training, special techniques for introducing new concepts into a specific cultural pattern in an acceptable fashion. This subject has been reviewed recently in several publications.^{2, 25, 30, 48}

Increasing Supply and Consumption of Animal Protein Products

In urban areas increased consumption of animal protein products can only be achieved through improvement of wage structures and general standard of living. Public authorities can, however, assist greatly by making available supplies of subsidized milk to groups particularly susceptible to protein deficiency such as pre-school children, adolescents and pregnant women. These subsidized products are best distributed through the appropriate child welfare and ante-natal clinics.³³

In rural areas every attempt must be made to increase livestock breeding through improved agricultural methods.¹⁴ All possible protein by-products from dairy farming, e.g. skimmed milk, should be put to the best possible use for human rather than animal consumption.

Alternatives to Milk Protein

In recent years, UNICEF has encouraged research into the use of vegetable protein mixtures as alternatives to milk protein.⁴¹ These alternative sources of protein are of great importance in areas where animal and dairy products are either too expensive or unobtainable. Considerable success has been achieved in this line of investigation and it is now established that appropriate vegetable protein mixtures can be as effective as milk protein for nitrogen retention and growth of pre-school children.^{20, 37, 40} A committee of FAO¹³ has suggested the use of so-called reference protein which contains an ideal pattern of amino-acids. With this reference protein as a guide mixtures of cereals and legumes or oil-seed meals can be devised, which provide a pattern of amino-acids as close as possible to that of the reference protein. In Central America a highly successful vegetable mixture (Incaparina) consisting of 58 per cent whole ground maize and

sorghum, 38 per cent cotton-seed flour, 3 per cent torula yeast, 1 per cent CaCO_3 and vitamin A is now going into commercial production for use as a protein food at an exceptionally low price.⁴⁰

A second approach is to improve the amino-acid pattern of cereal staples by providing the amino-acids that are limiting in a synthetic form. The nutritive value of cereals for children has been shown to be improved by this form of supplementation.^{3, 4, 38} Amino-acid supplementation does not, however, solve the problem of increasing total protein intake and is not at present a practical form of supplementation.

A third approach has been to add small quantities of animal protein to basic cereal diets. In this way, limited supplies of animal protein can be stretched much further. All indications are that this form of supplementation will prove most useful. For example, as little as 20 per cent addition of milk powder or 10 per cent of fish flour to a maize/pea flour mixture produces a protein that is equal to milk in measurable nutritive value.²¹ The animal protein supplements have the great advantage of improving not only the amino-acid pattern of the vegetable protein but also the protein vitamin and mineral intakes. It is commercially possible to produce very cheap foodstuffs along these lines and this might very well prove to be the most important means of preventing protein deficiency in a susceptible group.

A recent report has suggested, on the basis of animal work, that if the biological value of a protein is 60 or more, amino-acid supplementation is unnecessary providing sufficient protein is eaten.⁹ This is borne out in studies on convalescent cases of kwashiorkor,²¹ where it has also been shown that a vegetable mixture with a biological value of 70 is inefficient when compared to milk at protein intakes less than 2.5 g./kg./day. At intakes higher than this nitrogen retentions comparable to an isonitrogenous milk diet were obtained. It would appear that in the development of new protein foods a biological value higher than 70 should be aimed at to ensure maximum nutritive value at all levels of intake.

Attention to Protein Requirements in Medical Treatment

Medical practitioners can do much to prevent the development of severe protein deficiency by recognizing its earliest sign—failure of growth. This is most important when children present with gastroenteritis, pneumonia, or other infections.³³ Proper attention to dietary protein needs is an essential part of treatment if further protein deficiency is not to take place. Ill-health with vague indefinite

symptoms such as lassitude and vague pains and frequent minor infections may well mean sub-clinical protein deficiency.

Treatment of Kwashiorkor and Marasmus

Treatment depends very much on the degree of severity of the disease when it is diagnosed. Detection of pre-kwashiorkor or early marasmus and the institution of dietary measures before the full syndromes become manifest is the most effective way of ensuring a complete cure. The death rate of cases admitted to hospital in extremis may be as high as 25–60 per cent.²⁵

Dietetic Therapy. The essential element of dietary therapy is the provision of protein in suitable form and in adequate quantity. It is generally agreed² that milk is the most convenient form in which to supply protein. Skimmed milk has been widely used because of its low fat content but more recently some workers have found full-cream milk and vegetable oil supplements are well tolerated even in the early stages of therapy.^{12, 17}

A total protein intake of 2–5 g./kg./day is sufficient to promote cure.² In the first two or three days of therapy anorexia and a tendency to abdominal distension may necessitate an intake as low as 1–2 g./kg./day. If it is remembered that 1 oz. (30 ml.) of liquid milk contains 1 g. of protein the required amounts of milk for individual children can be easily calculated. Some investigators have advocated the addition of protein concentrates to milk to further increase protein intake. Although nitrogen retention increases with the higher intakes the clinical results achieved are no better than with the use of milk alone.³²

After 7–10 days appetite will usually have greatly increased and a mixed diet may be introduced to complement the milk protein and provide extra calories.

If necessary, cure can be achieved with the use of vegetable protein diets alone but these must be carefully chosen and skilfully combined. Vegetable protein content should be at least 20 per cent of the diet and a high intake insured because nitrogen absorption is not as efficient with these diets as on a milk diet.^{20, 37}

Vitamin concentrates are usually considered unnecessary in therapy except where there is definite evidence of vitamin A, D or C deficiency.^{6, 17}

Mineral supplements in the form of potassium chloride (g. t.d.½s.) are considered important in the first two weeks of treatment.⁴² After this time iron therapy should be instituted to correct the frequent concomitant malady of iron deficiency.⁴⁷

Resuscitative Therapy. Many children present at hospital with signs of dehydration resulting from diarrhoea. Intravenous fluid therapy must be resorted to in these cases even in the presence of oedema. In one series²⁷ mortality was reduced by 20 per cent with the sole addition of parenteral therapy to a standard regime of management. Blood may be given for severe anæmia.

Antibiotics. The frequent association of infections with kwashiorkor necessitates the administration of penicillin and sulphadiazine for at least the first seven days.⁶ Broad spectrum antibiotics should be used in specific infections for which they are indicated. It has been suggested that powerful antibiotics should be used routinely.^{43, 44} Intestinal helminths should be eliminated after the child has recovered rather than during the acute phase of the illness.

General Hospital Care. Personal, patient and tender care is of great importance in the handling of these children in hospital. In some institutions it has been found helpful to have the mothers admitted with the children.¹⁶

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CHAPTER 24

TRENDS IN INFANT NUTRITION

by

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THE fact that I have been asked to write about recent trends in infant nutrition is of itself significant of a trend. Not too many years ago the suggested topic would surely have been infant feeding. The concern of the pædiatrician of yesterday was to adapt the food to what was thought to be the delicate digestion of the infant. If he showed digestive symptoms, if he failed to thrive, it was because his tolerance for this or that had been exceeded. The art of feeding consisted in restricting the intake of the supposedly offending foodstuff until tolerance could be regained and at the same time giving enough food to keep the child alive. Sometimes this was successful, sometimes not, and often in desperation the physician abandoned science for Nature and turned to breast milk as a last resort.

All this changed with the advent of the modern era of nutrition in the years following World War I. Deficiency diseases were recognized in man and in animals, producing a great variety of symptoms. The concept of food intolerance and food intoxication waned; adequate nutrition was the clue to health. Efforts were centred on determining the essential foods and their quantitative requirements—for the growing child and for the adult; the objective was to supply enough for all individuals, even those who might have unusually high requirements. This goal has been pursued with great vigour. The development of nutritional science in the last three decades has been nothing short of extraordinary. Laboratories engaged in nutritional studies have multiplied and many clinical studies have been carried out. The number of nutrients essential for the human species has increased from a paltry dozen to forty and it would be a rash individual who would assert that we have reached the end of the list. Nutritional societies and nutritional journals have come into being and the newer knowledge has been passed on to the public by an army of dieticians and home economists, through school education and through industrial promotion techniques. Public health agencies

once preoccupied with the control of infectious disease have picked up nutrition. Standards for nutrient requirements have been set by governmental and quasi-governmental bodies, surveys made which show that these standards were not being met and literature distributed to correct this situation.

This development is a matter in which we can take pride. The enthusiasm to abolish malnutrition has not been misplaced. Much good has been done and much deficiency disease has been eliminated. Malnutrition is still an appalling problem in many parts of the world and the knowledge gained needs most urgently to be spread in these areas. Nevertheless, there are indications that in the so-called "technically developed" countries and in what we may call the "technically developed" population groups the enthusiasm for better nutrition may have overshot itself and that a more critical appraisal of the objectives and results of this effort are needed. The facts which have pointed to a need for reappraisal are the following. The efforts to increase vitamin intakes to levels that would protect *all* members of a population—even those with unusually high requirements—have not infrequently led to hypervitaminosis and in the case of the fat soluble vitamins there are indications that cases of hypervitaminosis now exceed those of deficiency in the U.S.A. The assumption that maximum growth is synonymous with maximum health and longevity is not supported by a considerable body of evidence from experimental animals.^{1, 2, 3} There are indications that the remote effects of diet may differ considerably from the immediate ones which have hitherto been our guideposts. Modern nutrition is credited with the fact that Americans are growing taller than their forebears,⁴ but the unexpectedly high incidence of atheroma in American soldiers killed in Korea⁵ raises the question as to whether the nutritious American diet may have been a contributing factor. Finally, the promotion of the essential nutrients has extended far beyond those which are of practical importance. This adds unnecessary cost to the diet and tends to foster dietary neuroses.

Recent thinking has been in the direction that optimal nutrition, which we all want, is not best attained by generosity in supplying all known essential nutrients. We have to consider the possibilities of harm from surfeits as well as from deficiencies. In the United States this thinking is reflected in the current nutritional standards published by the Interdepartmental Committee for Nutrition in National Defense,⁶ in contrast to the dietary recommendations of the Food and Nutrition Board⁷ which are concerned only with the avoidance of deficiency.

In the pædiatric age group the need for re-evaluation of some of our earlier tenets has also been felt. With the emergence of scientific nutrition breast milk lost much of its aura. No remarkable nutrients were found in it, and analysis showed that in many instances the margin above minimal requirements which it provided was small indeed. Furthermore, the composition of breast milk has proved to be less constant than had been believed. There is little variation in its content of protein and carbohydrate, but the composition of the fat has been found to reflect in considerable part the fat of the maternal diet^{8, 9} and this is true to some extent of the vitamin content also. Evidence was brought forward indicating that the premature infant needed more nitrogen than the full-term infant^{10, 11} and that the low protein content of breast milk was suboptimal for him.¹² The famous dictum of Oliver Wendell Holmes that these two orbs (the breasts) possessed more wisdom than the two hemispheres of the most learned professor's brain was quoted less frequently. And the query was raised—Why hadn't Nature provided enough vitamin D in breast milk to prevent rickets and enough iron to prevent anæmia? The virtues of maternal nursing were still appreciated but faith in breast milk as the ideal nutriment waned. Breast milk dairies went into a decline. It seemed possible that the learned professor could indeed improve upon Nature, particularly in the case of the premature infant.

The learned professor and his aid—the producer of clean and digestible cow's milk—have taken over to a great extent in many technically developed areas. In the north-eastern United States a recent survey by Meyer¹³ shows that 79 per cent of infants at the time of discharge from the hospital are exclusively bottle fed. Nearly all are fed on processed cow's milk, usually evaporated milk or proprietary formulas in evaporated form. The processed milks are all fortified with vitamin D and some of the proprietary products with vitamin C as well. The practice of introducing homogenized solid foods containing iron by the age of 3 months is almost universal. Those who deplore this trend find it hard to produce mortality and morbidity statistics to support their view and rest the case for breast feeding on psychological rather than nutritional grounds. The bottle-fed infant in a privileged society grows quite as well and is quite as free from disease as his breast-fed brother. Perhaps at the age of a year he weighs a little more, and certainly his development is quite satisfactory.

It may be pointed out here that artificial feeding with cow's milk as practised today has followed two distinct patterns, which may be

described as the traditional pattern and the humanized milk pattern (Table 1), both of which have their staunch advocates. The *traditional modification* of cow's milk, developed before the modern era of nutrition, consisted in diluting the milk and making up the calories by the addition of sugar. The dilution originally served the

TABLE 1

	<i>Protein</i> % of cals.	<i>Fat</i> % of cals.	<i>Carbo- hydrate</i> % of cals.	<i>Ash</i> %	<i>Ca</i> %
Cow's milk: Traditional type of modification with added carbohydrate	15	35	50	0.7	0.13
Cow's milk: A typical humanized preparation	10	43	47	0.45	0.08
Breast milk	8	50	42	0.3	0.03

purpose of reducing or avoiding curd indigestion, and the lowered intake of calcium and phosphorus made the product less constipating than whole cow's milk. Reduction in the fat intake was incidental, but was believed to be of value in an era in which the induction of fat intolerance was feared. The *humanized milk pattern*, developed in a number of proprietary products in various countries, involved a greater dilution of the original milk, further reducing the protein and mineral content; the calories were restored with fat as well as with carbohydrate, and the original butter fat was often replaced by a fat mixture richer in essential fatty acids. The important differences between the two types of feeding are the lower protein and mineral content of the humanized modification, not quite as low as that of breast milk but nevertheless approaching it.

Controversy prevails^{14, 15} over the nutritional merits of these two types of feeding, a controversy which is of interest because it involves certain fundamental concepts in nutrition. In the past it was believed that breast milk protein was superior to that of cow's milk in biological value and that for that reason more protein must be supplied when the latter is fed. This was undoubtedly the case when unprocessed cow's milk was employed, for much of the protein present in the form of tough curds escaped absorption. Recent work

has indicated, however, that the proteins of the two milks are nutritionally equivalent when processed cow's milk is used for the comparison.¹⁶ The most recent studies of the biological value of the proteins of the two milks, based on rat growth assays¹⁷ have shown no appreciable difference between them. Snyderman and Holt¹⁸ have studied the effect of the amino-acid pattern (aminogram) of the food on the rate of growth of premature infants, using a synthetic diet, obtaining closely comparable results with a breast milk pattern, a cow's milk pattern and the FAO reference pattern.¹⁸

It is not disputed that the minimal requirements of the infant for protein and minerals (particularly calcium) are met by the humanized milk preparations nor can it be stated that clinical differences have been discovered between the results of these two types of feedings. The controversy concerns the need for a margin of safety above the minimal requirement and also the significance of certain variations in body composition which result from variations in the protein intake. Such changes have been observed in experimental animals and there is evidence that they occur also in the human species. Advocates of the traditional type of formula take the position that a higher intake of protein and minerals offers a greater and hence more desirable margin of safety. Those who prefer the humanized type of formula maintain that the alleged margin of safety is in reality spurious.

The Concept of a Margin of Safety

A recent debate on this question by Elvehjem and King²⁰ makes interesting reading—Elvehjem taking the position that the minimum level of a requirement is the optimal and King arguing for the desirability of an increment above this. In part the difference of opinion is one of semantics. The minimal protein requirement will vary with the quality of the protein. If we define minimal requirement as that of a protein of high biological value such as milk we will obviously need a factor of safety when we feed a protein of lower biological value; more of the latter will be required. If the food is imperfectly masticated it is obvious that an increment will be needed to compensate for this. If the diet contains insufficient protein spacers—fat and carbohydrate—additional protein will be needed to supply energy. And if the diet is unbalanced at a particular meal, sparing will be inefficient and more protein will be required. In the case of the milk-fed infant, however, none of these situations prevails. The quality of the protein is high, the food requires no mastication, protein sparing is ample and the food does not vary

from meal to meal. The remaining argument concerns the desirability of ingesting more than the minimum requirement of a nutrient in times of health in order to provide a reserve for use in case of a subsequent shortage of that nutrient.

Much has been written about "reserve protein" and the need for maintaining "protein stores" but it seems that much of this concept will have to be revised²¹ in the light of recent studies. The facts of the case, derived mostly from animal studies, are the following. If one feeds growing animals various levels of protein, an animal fed on higher protein will have a body composition somewhat different from that of the animal fed low protein; his body will contain more nitrogen and less fat. The percentage of nitrogen in the fat-free tissue, however, will be identical. The nitrogen in the high-protein animal is distributed somewhat differently from that of the low-protein animal. Certain of the viscera, notably the kidney and liver and to a lesser extent the adrenal cortex, undergo hypertrophy and contain a higher share of the body nitrogen. There is evidence²² that this organ hypertrophy is a "work hypertrophy"—the kidney hypertrophies because it has more work to do; it has more urea to excrete. The liver has a greater load of amino acids to deaminate and the adrenal cortex has a greater task of gluconeogenesis from protein to perform. Do these hypertrophied organs actually serve as stores of nitrogen that are potentially useful in meeting subsequent situations of protein privation? An experiment to test this point was recently undertaken by Dr. Elias Halac in our department.²³ Rats were fed from weaning time to the time of maximum growth at two levels of protein—27 per cent and 64 per cent. Body analyses of sample animals showed that the higher protein diet yielded, as would be expected, a higher proportion of nitrogen and a lower proportion of fat; the liver and kidney exhibited the expected hypertrophy. Both groups of animals were then placed on a protein-free diet. Loss of weight (Fig. 1) was comparable in both groups and survival was unexpectedly long. When the experiment was finally terminated, however, the rats on the lower protein intakes showed a higher percentage of survivals. The higher percentage of nitrogen in the high-protein-fed animals did not function as a protein reserve. An explanation of these results is found in other studies that have been carried out in man as well as in animals. The turnover rates of certain proteins that have been measured, such as the plasma proteins, vary directly with the protein intake^{24, 25, 26} (Fig. 2). Since their level remains normal it follows that both protein anabolism and catabolism are increased. On withdrawal of dietary protein animals fed a high

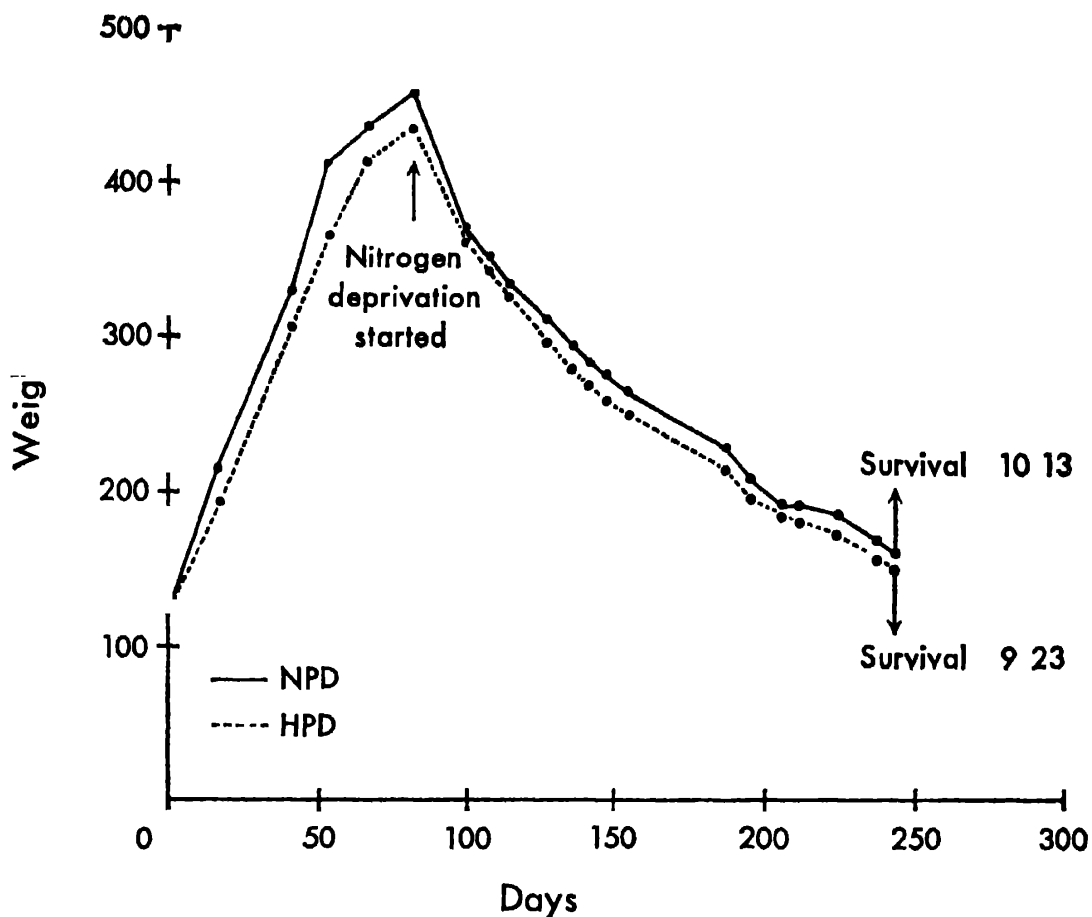


FIG. 1. Effect of nitrogen deprivation on weight curve and survival as influenced by prior protein intake. After Halac. HPD = high protein diet (64 per cent protein;) NPD = normal protein diet (27 per cent).

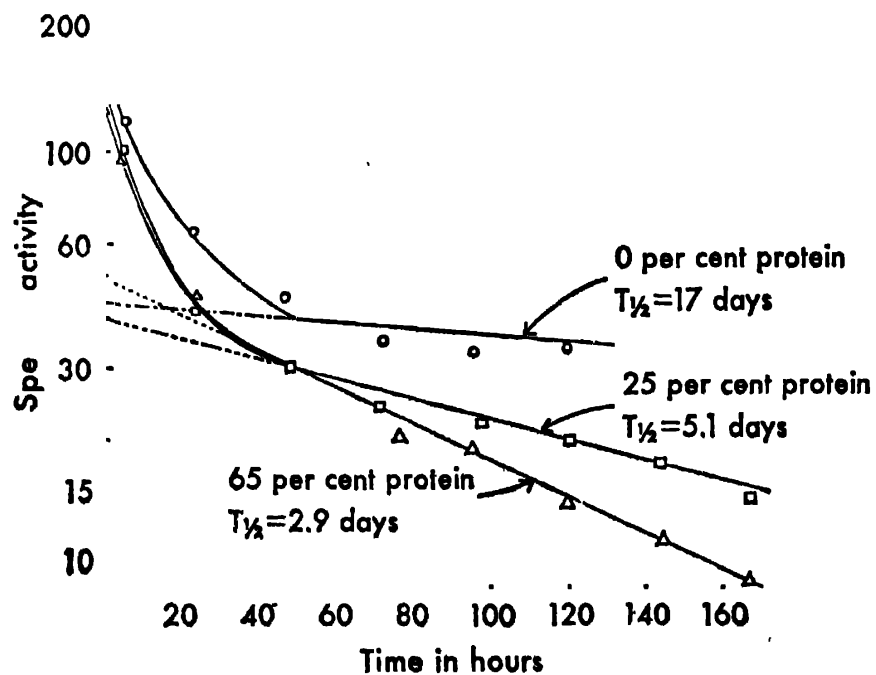


FIG. 2. Relation between protein intake and turnover of plasma protein in rats. After Steinbock and Tarver.

protein diet have been found to excrete more protein in the urine than those on a lower protein intake.²⁷ The higher rate of catabolism continues in the face of impaired anabolism and the additional nitrogen fails to function as a reserve. Experiments of this type need to be extended over a wider range of intakes before this conclusion can be unequivocally accepted. All that can be said now is that such evidence as is available fails to support the concept of a protein reserve.

How can the animal or the infant compensate for a period of food privation if he is to be fed only the minimal requirement? The answer to this question would seem to be to make up the deficit during convalescence from an increased intake and an increased ability to assimilate food *at that time* rather than from a reserve set aside during the preceding period of health. The minimum requirement for health is not necessarily the optimal requirement for convalescence.

In the foregoing discussion we have considered the possibility of creating stores or useful reserves of protein by the generous administration of dietary protein. Another phenomenon must now be considered in this connection—the extent to which *chemical maturation* of the body can be abetted by dietary protein. The chemical composition of the body changes steadily from early foetal life and during the early months of postnatal life. By and large this consists of an increase in the proportion of intracellular to extracellular tissue. The percentage of nitrogen in the body at birth is approximately 2 per cent. In the premature infant it may be considerably less than this. The percentage of nitrogen rises rapidly during the early months of life. According to Moulton²⁸ (Fig. 3) the adult figure of a trifle over 3 per cent is approached towards the end of the first half-year, subsequent changes being minimal. Direct analytical data bearing upon this point are, however, very limited for the human species.

It seems clear that in the first months of life, and particularly in premature infants, nitrogen retention can be increased by means of a high protein diet. Although Wallace²⁹ has pointed out an analytical error that would bias conclusions in such experiments, it seems that this error will not explain the magnitude of the differences observed. By the time the child has reached the age of 6 months it is difficult to demonstrate increased retention on an increased nitrogen intake. Harrison³⁰ was able to do so in only 1 of 5 subjects studied at this time of life. If the young infant and particularly the premature infant can be made more mature chemically by feeding him more protein it

would offhand seem a desirable thing to do. On the other hand the question may be raised: In making the infant more mature *chemically* with respect to nitrogen are we really making him *functionally* more mature? It is an unanswered question at the present time and one that surely needs answering.

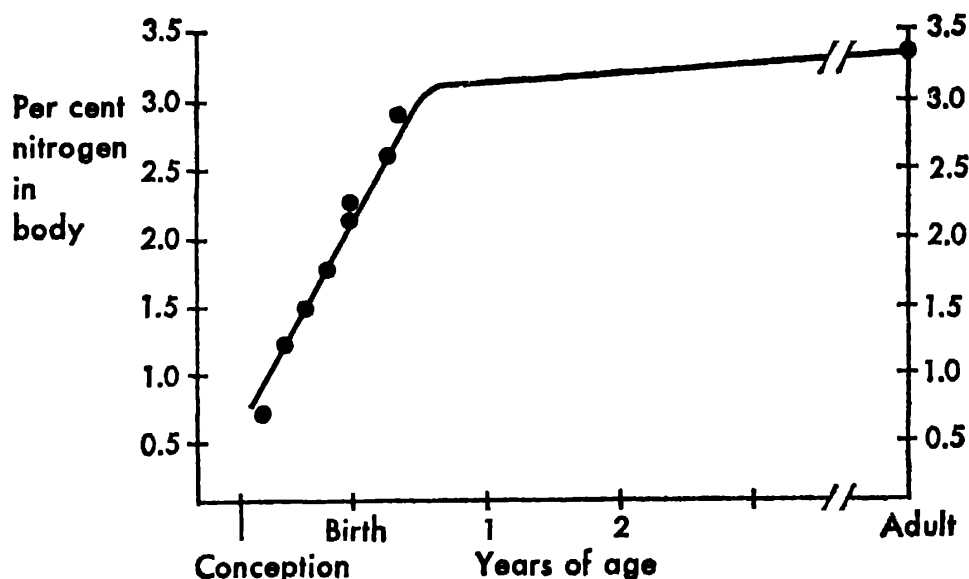


FIG. 3. Nitrogen content of human body at various ages.
After Moulton.

Some observations made in our clinic by Drs. Cusworth, Phansalkar, and others³¹ tend to cast doubt on the view that the increased nitrogen retention actually represents protein synthesis. It was found that during the early months of life the infant was able to accumulate considerable quantities of free amino-acids in his red blood cells, quantities several times as high as are found in older children and adults. Evidence from animals indicates that this phenomenon is not confined to the red cells but occurs in a number of other tissues. Christensen and his co-workers³² have explored it using an unphysiological amino-acid and have termed the phenomenon the "amino-acid hunger" of the cells in early life. Does this phenomenon account for the increased nitrogen assimilation with intake, and is this amino-acid nitrogen stored until the body is able and willing to use it for synthesis, as is the case with iron ingested in the early weeks of life, or can we really stimulate protein synthesis by protein intake? We do not know the answer. The optimum intake for the young infant is still to be ascertained. The fear that has been expressed that infants fed relatively low protein diets might be less efficient in producing antibodies is certainly not borne out by the excellent

reputation which breast-fed infants enjoy in regard to resisting infection. Dancis, Osborn and Julia³³ studied antibody formation in bottle-fed infants at two levels of protein intake, providing 10 per cent and 20 per cent of the calories respectively, and failed to observe differences in the response to diphtheria and tetanus toxoid.

Before leaving the comparison between the traditional and the humanized formulas we might mention again that the former supply more minerals, including calcium. The need for a generous intake of calcium to make sound bones and teeth has been widely stressed by nutritionists, despite the fact that calcium deficiency is virtually unheard of in well-developed countries and that students of caries no longer attribute this disorder to a lack of calcium. The Food and Nutrition Board of the National Research Council has until recently recommended intakes of calcium well beyond those provided by breast milk. The enthusiasm for calcium has been prominent in the minds of many adherents of the traditional type of infant formula, but there are indications that this is waning. There is evidence that increasing the calcium intake of the infant will increase calcium retention, but that this is desirable is not demonstrated. Observations in experimental animals³⁴ have shown that increasing the calcium intake increases catabolic as well as anabolic processes in which calcium is concerned and that these may continue well after the high intake is discontinued. An excellent symposium covering this subject has recently been published.³⁵

In closing this brief discussion of a few of the recent trends in infant nutrition it might be pointed out that although breast milk has lost its aura and mystery and although we have learned to dispense with it with impunity, the attempts to better it by increasing the quantity of this or that nutrient have not as yet been demonstrated to have value, and the trend in recent years has been a return toward the breast milk formulation in artificial feeding. Future work may reverse or accentuate this trend. There have been many such reversals in the slow and painful path by which knowledge is gained. It does not behove us to be over-confident in regard to our present wisdom, but rather to appreciate the gaps in our knowledge and to attempt to fill them. Some of the gaps that need to be filled have been pointed out.

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CHAPTER 25

EFFECTS OF ALTERED NUTRITION ON THE SKELETAL SYSTEM ; THE REQUIREMENT OF CALCIUM IN MAN

by

W. P. U. JACKSON

Childhood Malnutrition Including Its Relation to Rickets

MCCANCE and his co-workers in 1946⁵⁵ showed that German children in an orphanage, who were known to have been on a low-calorie diet for several years, were shorter and lighter than English and American children of the same age. Their bony development ("bone age") was backward. After a year of unlimited calories, they had almost caught up with their Western counterparts. McCance quotes other evidence from man and animals to show that under-nourishment leads to smaller children while overfeeding may, to some extent, force the rate of growth and development of bones. If the latter is true, a likely mechanism would appear to be via an increased insulin production from stimulation of the pancreas by the excessive food intake.

The Gillmans²⁹ state that newborn and infant Africans are significantly smaller than European infants because of malnutrition, and that in such infants rickets is common. In patients who died of "infant pellagra" (kwashiorkor) changes characteristic of rickets or scurvy were almost always seen. In adult pellagra they found "osteoporosis" (this statement is not documented). In children who were autopsied at the Medico-legal Laboratories in Johannesburg they found over 50 per cent to show severe rickets of the costochondral junctions. They remark on the high incidence of rickets in various tropical and subtropical countries, and suggest that malnutrition in such areas leads first to changes in the skin which either prevent the penetration of ultra-violet light or alter the metabolism of steroids. We cannot, however, agree that skin disorder has much to do with rickets, at least in Cape Town. The Gillmans conclude that a multiplicity of factors contribute to "bone diseases among the Africans" [*sic*]. However this may be, small doses of vitamin D are

capable of curing their rickets, and no other bone disease has been shown to exist on a national scale.

Jones and Dean⁴⁴ have studied the development of the bones of the knee in children suffering from kwashiorkor. Healthy children of members of the African staff of the Agricultural Research Station near Kampala were likewise examined as controls; 75 children with severe kwashiorkor were X-rayed on admission to hospital. In both boys and girls great retardation was found; so much so that there was almost no overlapping between the healthy and the malnourished groups. The bones of the children with kwashiorkor were smaller, poorly calcified and showed diminished trabecular pattern, compared with the controls. A high proportion showed other abnormalities: thinned cortices, faintness of zones of provisional calcification at the metaphyses, growth arrest lines, and irregularity of calcification of the epiphyseal margins.

Measurement of height or of subischial length correlated closely with the degree of retardation of skeletal development. This retardation was much greater than could be accounted for by the known length of the illness, and appeared rather to measure the length of period of malnutrition.

These findings corroborated the histological studies of Higginson³⁷ who observed a marked depression of bone (rib) growth in children suffering from kwashiorkor. This was not seen in children who were ill with other conditions. Biopsy examination revealed generalized osteoporosis, rather than the wide osteoid seams of rickets.

It would appear to be the general opinion, with which we concur, that children with kwashiorkor do not usually have rickets, despite the Gillmans' claim.²⁹ It is, of course, frequently stated that only children who are actively growing can show rickets. We¹⁶ have certainly observed that children with rickets are well below the normal mean in height, but we admit the possibility that this deficiency of growth may have started only after the rachitic condition appeared. Wayburne and Dean have recently⁸⁶ made similar observations, and conclude that "growth failure . . . will not protect against rickets" [*sic*].

There can be no doubt, however, that rickets is common in tropical and sub-tropical communities when properly looked for, as can be seen from the reports of Williams⁸⁹ from Singapore, Feldman²³ from Johannesburg, Griffel and Winter³⁰ from Israel, and Stransky and Ocampo from Manila.⁷⁴ Even from Baltimore in the United States, Follis and co-workers²⁵ reported that nearly 50 per cent of their autopsied cases in the first two years of life had definite

histological rickets, with an even higher incidence in the Negro. One wonders, however, whether some of the histological features which they describe as rachitic cannot really be physiological, especially since they found no greater incidence in premature infants—contrary to all clinical evidence.

Vitamin D

Deficiencies and Requirements. Osteomalacia caused by insufficient vitamin D intake in adults is a rarity in civilized countries, but is nevertheless still seen in Northern, relatively sunless climates, in old, undernourished people,⁶⁰ in vegetarians⁵⁴ and in other special circumstances (e.g. nuns in convents in wartime).⁷⁸ The final diagnostic criterion in such cases is the cure of their bone disease by ultra-violet light or a few thousand units of calciferol (vitamin D₂).

In the South African Bantu, not only is the intake of calcium very low, of phytate high, and the Ca : PO₄ ratio low, but there is practically no vitamin D at all in their diet.⁷⁹ Nevertheless rickets and osteomalacia are not common in the rural Bantu (as opposed to the Gillmans' findings in urban Bantu in Johannesburg, as discussed above) and the mineral density of the skeleton is probably no lower than that of the European, according to Walker.⁷⁹ (No good statistical study of rickets in the rural Bantu has yet appeared, however.) Walker suggested that the extra exposure to sunlight in Africa and Asia might allow a better use of the small amount of calcium in the food in these continents than could be found in the northern, less sunny countries. This idea would appear to be at variance with the advice of the MRC Conference on Hypercalcaemia which recommended that a daily intake of 400 international units was adequate during infancy.¹³ This figure is generally taken as adequate for all times of life by most nutritionists. That sunlight is an important factor, however, is strongly suggested by an investigation into the high prevalence of rickets in the coloured (half-caste) population in Cape Town.¹⁶ The young children in this group are frequently kept indoors, and the negative correlation between rickets and hours of sunlight exposure was much closer than that between rickets and calcium intake or breast feeding, and was very different from that found in a control non-rachitic group. This corroborates the old observations of Maxwell⁵³ and Snapper⁷¹ who considered that the sunlight in South China prevented the ordinary women from getting the osteomalacia seen in their counterparts in North China, and likewise prevented their children from getting rickets.

Although in general the addition of a few thousand international

units (I.U.) of vitamin D makes no difference to the calcium metabolism or apparent requirements in adults, yet Ackerman and Toro¹ claim to have found a distinct increase in calcium retention in 6 elderly men following the administration of 25,000 I.U. daily for 40 days. They found that this effect disappeared 40–60 days after discontinuation of the vitamin. Albright and his co-workers⁴ however, found no improvement in calcium retention from the use of vitamin D in elderly patients with osteoporosis.

Excessive Intake. The classical variety of hypervitaminosis D is encountered in adults who have been receiving something of the order of 250,000 units (about 6 mg.) calciferol or more per day for long periods. It is characterized by hypercalcaemia with its attendant symptoms, and extraosseous calcification, including renal stone formation. The toxic effect on bone is, interestingly enough, decalcification—more exactly a poor mineralization of newly formed bone rather than actual osteoclasia.³² Recently de Langen and Donath¹⁸ have shown that large doses of calciferol in rabbits produce a rise in serum cholesterol and atherosclerosis—they wonder whether a comparatively smaller intake in man over long periods might be implicated in human atheroma.

“Idiopathic hypercalcaemia” of infants has been described in two forms, the mild variety which ends in complete recovery⁴⁷ and the severe form, in which the brain, kidneys, heart and bones become irreversibly damaged.^{22, 69} The bone disorder is an osteosclerosis, affecting particularly the base of the skull, vertebrae, long bones and epiphyses. The skull is small and the facies abnormal. Hypercholesterolaemia is also found. It is likely, but not yet completely certain, that these two conditions represent different degrees of the same disorder, which is produced by an excessive intake or undue sensitivity to vitamin D. Thus, infants with idiopathic hypercalcaemia had been receiving as much as 4,000 I.U. per day (since the fortification of dried milks and cereals with calciferol in Britain); an abnormally high intestinal absorption of calcium was found when balance studies were performed; and relapse was produced in one infant, who was in a state of remission from the mild form of the disease, by giving 10,000 units of calciferol daily for 10 days.¹¹

There are, however, certain features of idiopathic hypercalcaemia which are unlike those of classical hypervitaminosis D. These include a high phosphate retention with hypophosphaturia, low levels of serum and urinary citrate²⁶ and the osseous manifestations. Fellers and Schwartz²⁴, in North America, investigated 3 cases of the severe form in detail, and, among other features, found excessively

high vitamin D levels in the serum by bio-assay. These high levels were still present up to 14 months after removal of as much vitamin D as possible from the diet. They suggest that the vitamin-D-active substance in the patients' serum was in fact not the natural vitamin D but another sterol with antirachitic and toxic effects. Perhaps relatively minor excesses of vitamin D₂ (calciferol) can produce the hypercalcaemic disease in infants who are born with some error in that part of their sterol metabolism concerned with vitamin D. It is believed by many that the incidence of the disease has fallen since the Cohen Committee¹³ advised that the levels of vitamin D in national cod liver oil, national dried milk, and infant cereals, should be considerably reduced.

It seems not impossible that there is such a natural variability in the requirements and the sensitivity of infants to vitamin D, that we must put up with rickets on the one hand or hypercalcaemia on the other. Stated somewhat differently, Fanconi²¹ recognizes, "a series of pathological conditions in childhood which are differentiated by their completely different reactions to vitamin D. At one extreme lies vitamin D resistant rickets; at the other, chronic hypercalcaemia" [*sic*].

Conditioned Deficiencies Occurring in Malabsorption Syndromes. The rickets or osteomalacia which may occur in idiopathic steatorrhœa, sprue or coeliac disease, or, uncommonly, in pancreatic disease, is generally stated to be produced through a lack of absorption of vitamin D, which, being fat soluble, is excreted in the faeces together with the unabsorbed fat. This story is *a priori* unlikely, since even in severe malabsorption states, some 60–80 per cent of fat is in fact still absorbed. Dent¹⁹ has actually found that vitamin D by mouth is just as active in such states as vitamin D by injection. Badenoch and Fourman,⁷ however, investigated 6 patients with a malabsorption syndrome and osteomalacia by means of balance studies in 2, and by following the effects of treatment in the others. They found that 10,000 units of vitamin D daily by mouth did not improve the absorption of calcium, whereas the same dose parenterally, or 50,000 units orally, did cause improvement of absorption provided the intake was high. Healing was slow even with parenteral vitamin D and large doses of calcium by mouth. It appears that there may be two (or more) factors responsible for the osteomalacia: (1) deficient absorption of ingested vitamin D, which may arise from actual destruction of the vitamin in the bowel, rather than its elimination together with fats, and (2) an internal factor in this disease which tends to inhibit the normal efficiency of vitamin D.

Steatorrhœa may occasionally follow gastric operations, and osteomalacia as a consequence of this has been described, after both partial gastrectomy and gastroenterostomy.^{8, 64, 66} The latter authors suggest that any patient who complains of multiple aches and pains after gastric surgery should be suspected of having osteomalacia.

The osteomalacia of steatorrhœa may lead to secondary hyperparathyroidism¹⁷ with bony changes of osteitis fibrosa superimposed on the osteomalacia. The stimulus to the parathyroid hyperplasia is believed to be the low level of serum calcium. It is uncertain whether ordinary D-lack rickets produces real parathyroid hyperplasia, though it is believed that the parathyroids in this condition frequently maintain the level of serum calcium within the normal range and may also produce the characteristic reduction of serum phosphate.⁵⁹

Atkinson, Nordin and Sherlock⁵ described the type of bone disease present in 12 cases of chronic jaundice, mostly with extra-hepatic obstruction, of 3 months' to 8 years' duration. All who were tested had steatorrhœa. Osteomalacia was diagnosed in 7 on the basis of X-rays, biochemical changes, histology and a decreased excretion of infused calcium. In 2 there was a mixture of osteomalacia and osteoporosis. Calciferol in large doses cured the osteomalacia, but not the porosis. In 3, osteoporosis was present alone, and in 1 of these a balance study showed a high calcium excretion on a low intake. Theoretically such patients might suffer from protein, calcium (and phosphorus) and vitamin D depletion, at least, so that, while the osteomalacia was almost certainly produced by mal-absorption of vitamin D, the mechanism of development of the osteoporosis was less clear. Secondary hyperparathyroidism has not, as far as I know, been reported in the steatorrhœa of jaundice.

Biliary cirrhosis has been found to lead to osteomalacia also by Ahrens *et al.*³ (with poor documentation) and by Snapper *et al.*⁷¹

Vitamin C

Irving⁴¹ and Weinmann and Sicher⁸⁷ have recently reviewed the relation of vitamin C to bone and tooth growth. In scurvy, experiments with S³⁵ have indicated that there is a decreased formation of chondroitin sulphate in the cartilage. Perhaps a more important review of the subject has been written by Bourne, which included a consideration of his own histological work.¹²

Grusin and Samuel³¹ believe that idiopathic osteoporosis in the Bantu is caused by chronic scurvy or repeated attacks of acute

scurvy. They found 14 patients with osteoporosis under the age of 60 in 1 year in a single hospital. Eleven of these had evidence of scurvy. They consider the association "so striking that it amounts to presumptive evidence of a common cause" [*sic*]. However, treatment with vitamin C for long periods did not appear to be of value, since at least 7 showed progressive deterioration. Unfortunately no balance nor bone accretion rate studies were performed. The single figure which illustrates their article is interesting, since a completely flattened vertebra (lumbar 3) is shown. In my experience this is not typical of osteoporosis, and suggests rather some infiltrative process.

Protein Deficiency Disease of Bone—Does it Exist?

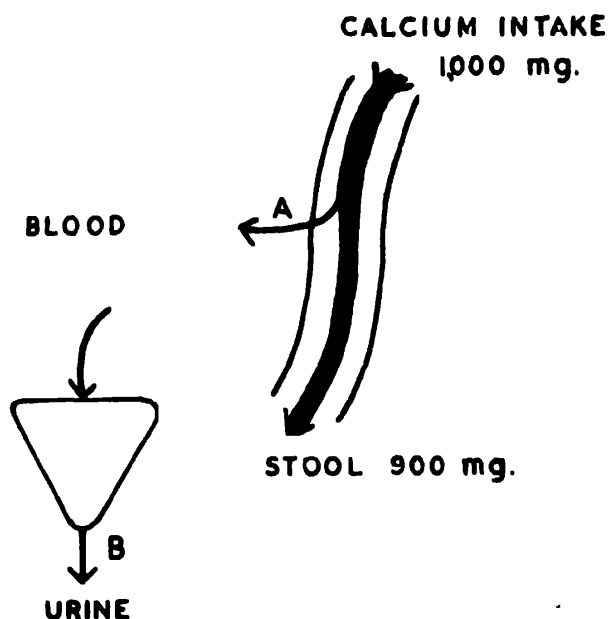
Osteoporosis is generally believed to be caused by a defect in the formation of the proteinous matrix of bone. A deficiency of dietary protein should, then, lead to this condition. However, in states of clinical osteoporosis there is very rarely any evidence of such deficiency; the "hunger osteopathy" of wartime undernutrition was osteomalacia and not osteoporosis; and a high-protein intake has not been shown to be curative of any bone disorder. In the condition known as "idiopathic osteoporosis", occurring in young people,⁴ there may be some beneficial effect in certain cases from the intravenous infusion of human serum albumin, but this highly artificial treatment cannot be claimed as proof of any dietary deficiency. The possible ætiological features of this strange condition are considered in detail by Jackson.⁴² Urist⁷⁷ summarizes succinctly the evidence with regard to the ætiology of the common osteoporosis in elderly people.

In the Minnesota experiment on semi-starvation⁴⁵ no demineralization was observed in 6 months—but this would not be expected in so short a time. Linder, Jackson and Linder⁴⁸ have argued that a massive resection of the small bowel may produce a state exactly comparable to that of simple undernutrition. Their most important patient, Toni, developed clear-cut radiographic evidence of demineralization after 3½ years, with no biochemical nor histological features of osteomalacia. This was probably osteoporosis, but even so there is no proof that protein deficiency was the cause. Balance studies indicated a poor absorption of both nitrogen and calcium.

Basic Fundamentals of Calcium Balance

Before any discussion of calcium requirements or deficiencies, it is essential to have a clear picture of what happens to the ingested calcium of the food. On a normal "civilized" intake of say 800 mg.

per day in the adult, the total net excretion (stools and urine, omitting the negligible amount lost in sweat, etc.) equals the intake (Fig. 1), provided the subject concerned has been on the same diet for a long period* and is in a good "static" metabolic state. Now the urinary calcium excretion in normal subjects is extraordinarily variable as between individuals (25 mg. to 450 mg. per day) but remarkably constant for the same individual on a fixed intake, and



A (Net absorption) = B, about 100 mg. per day.

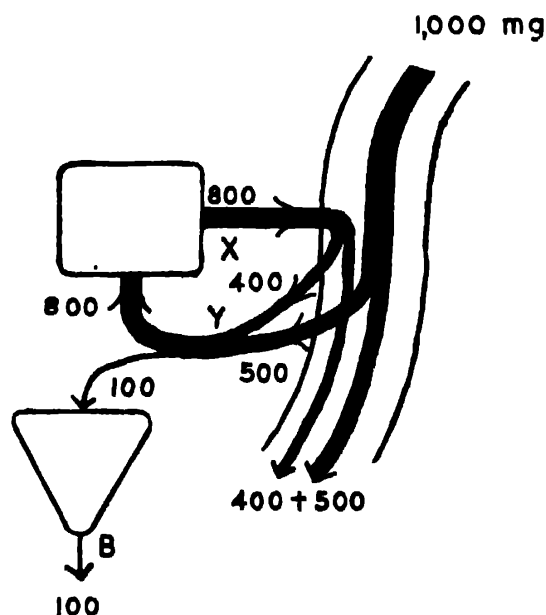
FIG. 1. In this normal man, the urinary calcium has been taken as 100 mg. The apparent absorption of intake is 10 per cent.

even relatively constant on vastly different calcium intakes.^{38, 46, 52, 58} It follows then, that, in our balanced individual, the net intestinal absorption equals the urinary loss (Fig. 1), and that this also varies enormously among different subjects. The person with 40 mg. of daily calciuria will absorb 5 per cent while the person with a daily urinary calcium of 400 mg. has a net absorption of 50 per cent. (This range is wider than that normally given, but is correct both logically, and from our own studies.)

The net intestinal absorption (intake minus stool calcium) is a measure of the calcium absorbed from intake plus intestinal secretions (Fig. 2). The amount of calcium in these secretions has been estimated by several workers at around 500–800 mg. per day (re-

* The length of time needed for equilibration to changed calcium intake is uncertain. In short-term experiments it may be taken as 10 days, but if "slow adaptation" really occurs (see later) the correct period should be months or even years.

viewed by Nicolaysen^{57, 58} and Malm.⁵²). Recent estimates, using Ca^{45} , have suggested a much lower figure, nearer 200 mg.^{9, 14} However, balance data have been reported over periods of weeks in which the faecal calcium has been higher than the intake by 500 mg. per day or more.⁵² This direct finding indicates that in some subjects at least, the intestinal juice calcium cannot be less than 500 mg. per day.

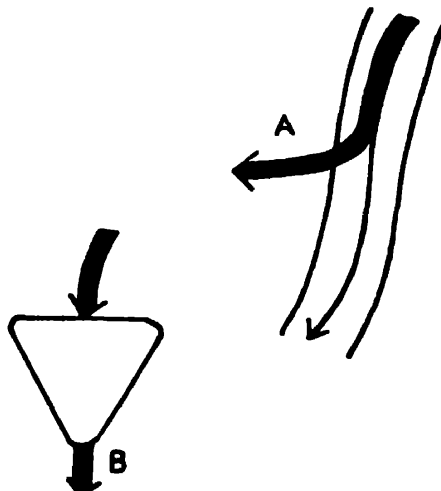


$$Y \text{ (Total absorption)} - X \text{ (Gastro-intestinal secretions)} = B$$

FIG. 2. The same man as in Fig. 1, including gastro-intestinal secretions, X , assumed here to be 800 mg. Taking this into account the *true* absorption of (intake plus secretions) is 50 per cent.

It is clear from the above considerations, that the faecal calcium is far more a function of the intake than is the urinary calcium, and it is not surprising that the graphic relationship between the ingested and faecal calcium is linear (reviewed in detail by Malm).⁵² On the other hand the net intestinal absorption may be considered as a function of the urinary output, so much so that it is difficult to avoid the conclusion that the absorption is in some way governed by the amount of the urinary loss in normal individuals and in a number of disease states (Fig. 3).⁴³ In this connection Nicolaysen⁵⁷ has pointed out that there must be some endogenous factor which controls calcium absorption, and causes it to increase in times of bodily need (Fig. 4) (e.g. growth spurts in children, after fractures, after parathyroidectomy in hyperparathyroid bone disease).

**OVER-ABSORPTION WITH HYPERCALCIURIA
(VITAMIN D, SARCOID, IDIOPATHIC HYPERCALCIURIA).**

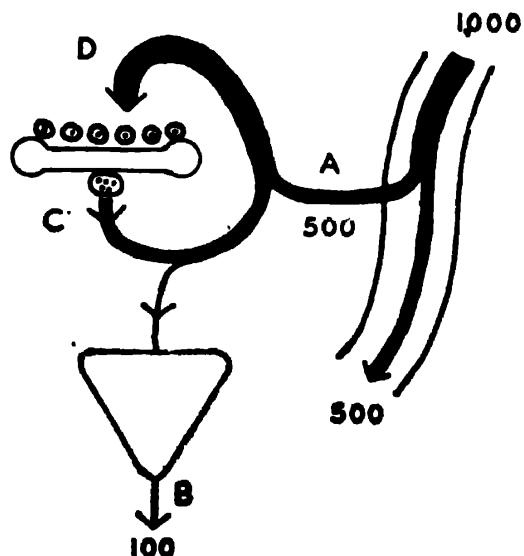


$A = B$ (\therefore No decalcification)

is A compensating for B? (see next figure).

FIG. 3. This figure also applies to a normal person with unusually high urinary calcium (B). He is not in negative balance because of the high percentage intestinal absorption (A).

**GROWING CHILD, AFTER FRACTURES, OR DURING
RECALCIFICATION**

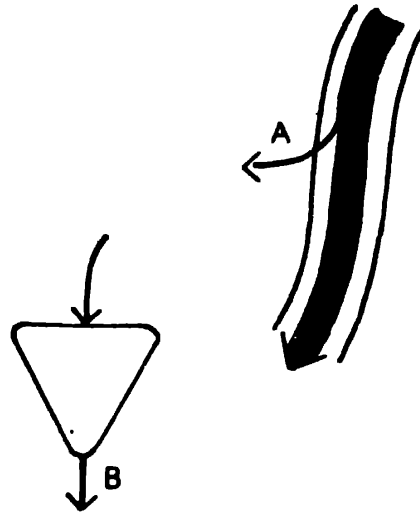


$A > B$ (i.e. Positive balance).

$D > C$ (i.e. Increased bone accretion).

FIG. 4. When the skeleton needs calcium, other factors allowing, the percentage intestinal absorption (A) increases, so that more calcium may be deposited in bone (D) than is resorbed (C). It may be presumed that this happens during recovery from lactation.

The initial response of a normal individual to a raised calcium intake is a highly positive balance, with a calcium retention which lasts 5–10 days, after which equilibrium again appears to be restored with a raised faecal calcium (reduced percentage absorption) (Fig. 5). The retained calcium must be deposited in bone (99 per cent of all body calcium is in bone). However, it is not today thought of as entering into the basic structure of bone, but rather as entering the calcium



Little increase in B.

(A may > B in acute phase; soon A = B).

FIG. 5. A normal person on high calcium intake. The extra calcium in the food is almost all excreted in the faeces, when not needed by bone. The urinary increase is much less.

“exchangeable pool”; which may be considered as a sort of calcium reserve. The size of this pool, as estimated by Ca^{45} and strontium studies is about 5 g. in normal adults.^{27, 61} The very existence of this “pool” would suggest that there is no valid reason to believe that a state of negative calcium balance is in any way deleterious *per se*, provided it does not continue for too long.

Calcium Requirements

In Adults. In 1953 the Food and Nutrition Board (U.S.A.) revised the recommended daily allowance of calcium and decreased it for adults from 1.0 g. to 0.8 g. Hegsted³⁴ points out that there is no good evidence in favour of such a high intake. The figure is based almost entirely on short-term balance studies, which do not necessarily bear any relation to true requirements, since a net negative balance is no logical indication of increased need. Neither does clinical observation

support this figure. Walker⁸² has remarked that most people of the world live, from weaning, through pregnancies and lactations, on an intake which is not only very much lower in calcium, but also contains the apparently bad calcium to phosphorus ratio of 1 : 10. Yet no syndrome of dietary calcium deficiency has yet been recognized in man; (this statement may need modification in the light of the theories of Whedon and of Nordin as mentioned later, page 310).

In any event, it is quite uncertain how calcium requirement should be calculated; how it differs in adults of different age, weight, height or body build. Malm discusses this problem in detail and concludes that it may be most accurate to use the fat-free body mass or skeletal mass. I doubt whether there is much advantage to be gained by any particular method, in view of the enormous individual variations in absorber-capacity (see later), and in urinary calcium output (which, over a long period, in a "balanced" subject must equal net intestinal absorption).

Sherman and his associates⁷⁰ found beneficial effects in rats from a rather high calcium intake, but these effects were not uniform and can certainly not safely be translated into human requirements. In this connection the work of Henry and Kon³⁶ is extremely interesting and suggests a new dietary principle. They showed that rats could become adapted to low-calcium intake and would then be more resistant to calcium depletion in old age. Gerschoff and co-workers²⁸ have confirmed this finding in dogs, showing that those animals who were habituated to a low-calcium intake could maintain balance indefinitely, whereas those who were used to a higher intake could not rapidly adapt to a lower one. Furthermore both groups of workers found no difference in skeletal calcium content between the high-calcium-intake animals and the low-calcium-intake animals. If this has any bearing on human nutrition, it would appear to indicate that adaptation to a low intake might afford some protection against the decalcification of old age. In other words, some "nutritional stress" may actually be of value in the long run in conditioning the body to withstand future deprivations. A similar idea is contained in the work of Boda and Cole,¹⁰ who showed that cattle may be protected from milk fever by feeding them a low-calcium diet before parturition.

McCance⁵⁴ clearly discusses the "calcium requirement paradox"—namely the frequency with which a severely negative balance can be produced by a low-calcium intake and/or high-phytate diet even after a prolonged period,^{56, 88} in contrast to the apparent absence of any evidence of calcium deficiency in the many parts of the world

where a low intake is general and permanent.⁵⁵ There is no good evidence that the bones of most of these people are smaller or contain less calcium than those of better fed races, or even where this is so, there is no evidence that the calcium intake is the cause of a smaller skeleton.⁸³ (The Ceylonese, according to Nicolaysen *et al.*⁵⁸ do have a much lighter skeleton than Europeans.)

McCance finds no good proof that humans can adapt to a lowered calcium intake. In particular he dismisses the long-term balance studies of Walker *et al.*⁸⁵ on the basis that the only three subjects involved were all good calcium absorbers before the experiment began. It seems to us, however, that this is in fact equivalent to adapting to a low intake—in other words there may be a high proportion of people who will rapidly regain their balance equilibrium on a low intake—we may say that they adapt rapidly. Perhaps some adapt more slowly (this is what McCance doubts) and some little or not at all. McCance makes the interesting suggestion that these “poor absorbers” (or “non-adaptors”) have actually been “bred out” of the low-intake races—being less fit to survive in the Darwinian sense—on the assumption that the standard of calcium absorption is an inherited characteristic. In this connection, Hegsted *et al.*³⁵ found that adult Peruvians who had lived upon low-calcium diets for long periods required only 100–200 mg. of calcium per day to maintain balance. Whether they were “good adapters” or congenitally “good absorbers” from the beginning is, of course, uncertain. Nicolaysen reviewed the evidence concerning adaptation to low-calcium intake up to 1953, and more recently Olé Malm, working in Nicolaysen’s department in Oslo, has made an important contribution⁵² which goes some way to answer McCance’s doubts and queries. Normal, human, male, adult, volunteer prisoners were used (age range 20–69). All but 4 of the 26 subjects were kept on a diet containing 940 mg. of calcium, 1,800 mg. of phosphorus (phytate-free) and not less than 200 I.U. vitamin D per day, and were studied for not less than 6 months. Twenty-two were then transferred to a so-called low calcium intake of 450 mg. with about 1,400 mg. of phosphorus, for prolonged periods of time (average 240 days).

Of the 26 men studied on the low calcium intake, 3 were in balance during the whole period (“good absorbers”), another 3 remained in negative balance for the whole period without any indication of adaptation, while the remaining 20 showed an initial negative balance for several weeks, followed by a distinct improvement in balance after variable periods, often of 70–100 days. There seems little doubt that Malm’s findings and conclusions are valid—perusal of the protocols

and exact figures indicate their unquestionable statistical significance. Adaptation, then, to calcium intakes *of this level*, certainly seems to be the rule, although it is not invariable, and some subjects who, partially adapted, remained in negative balance, although this was of a lower order in later weeks than initially.

The process of adaptation is shown by a decreasing faecal calcium, without much change in urinary output (Figs. 6 and 7). Although a small proportion of people did show significant and important falls

(ACUTE) LOW CALCIUM INTAKE

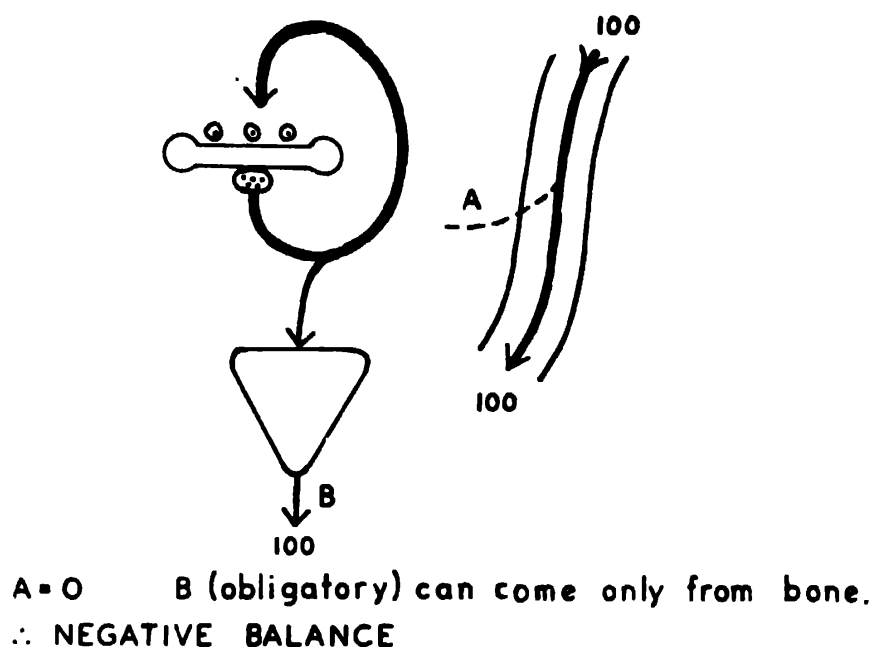


FIG. 6. A sudden drop in calcium intake (here, to 100 mg. per day) leads to a negative balance, in which the obligatory urinary loss (B) must come from bone.

in urinary calcium on a reduced intake, the mean fall in urinary calcium when the intake was reduced from 940 to 450 mg./day was not statistically significant. The reduction in faecal calcium could be produced by an increased absorptive capacity or a reduction in calcium secreted into the intestine. The latter mechanism would not appear to be likely, but the evidence against it is entirely indirect at the present time. Certainly we have found that the faecal calcium on low intake may be considerably lower than the calculated faecal fraction of the intestinal juice calcium, assuming the gross percentage absorption on normal intake to apply to the latter. This may merely reflect an increased absorption of the secreted calcium.

Unfortunately Malm's work does not provide a complete answer to our various questions, since the intakes used were not low enough to be equivalent to those found in the underprivileged races mentioned above, nor are children, pregnant or lactating women considered at all.

LONG-TERM LOW CALCIUM INTAKE.
As in Bantu.

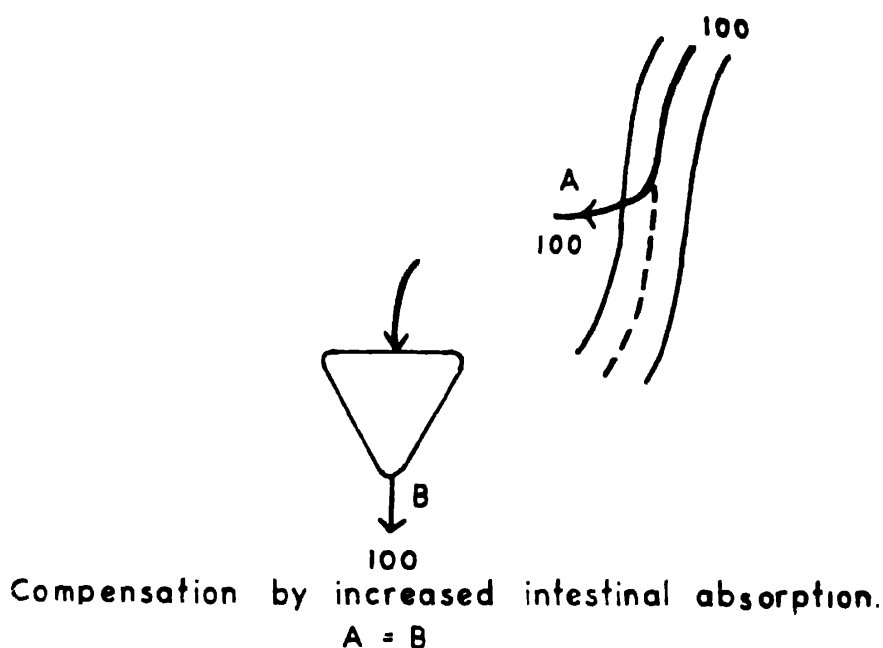


FIG. 7. Depending upon the individual, as adaptation to low intake occurs, the percentage absorption rises so that equilibrium may be re-established.

In Childhood. It appears equally difficult to say how much calcium is required by children, since the fundamental work of Stearns⁷² suggests that, within limits, the more they get, the more they retain. They appear capable of storing calcium in their skeleton, particularly in periods just prior to the growth-spurt, and then using it for real bone formation when necessary.

A simple calculation, based on the assumption of 1 Kg. of calcium in the adult body, growth up to 16 years, and neglecting the amount at birth, indicates a mean retention of something under 200 mg. per day. Since children are, apparently, much better "absorbers" than adults, there would seem little necessity to augment their calcium intake or to insist upon large quantities of milk in any reasonably fed community. The striking observations of Aykroyd and Krishnan,⁶ who succeeded in increasing the rate of growth of Indian school

children by simply adding calcium lactate to their customary diet must, however, be remembered. Furthermore, Holemans and Lambrechts, in the Belgian Congo,³⁹ found no adaptation in African children when their calcium intake was reduced from a mean 22.8 mg. per kg. per day to 11.2 mg.—the mean stool calcium actually rose! It is likely, then, that children in races with very low intake might well benefit from an increase which brought the level up to at least 500 mg. per day.

Walker,⁸⁰ however, criticizes the conclusion of Aykroyd and Krishnan that their calcium supplementation *per se* produced the increase in height and that this necessarily indicated a preceding calcium deficiency. He further summarizes the evidence in favour of the thesis that pure calcium deficiency leads to stunting of growth, and finds it to be unacceptable and incomplete. More exact work has shown no influence of calcium supplementation on growth, when the diet has otherwise remained constant. He believes that "the critical intake of calcium, below which retardation of growth occurs, lies *below* the wide range of calcium contents of everyday diets consumed in different parts of the world" [*sic.*]. This is not to say, though, that more calcium in the diets of underprivileged children is not desirable, *together with* more protein and other essential nutriment.

The subject of calcium requirement in infancy is discussed by Holt in Chapter 24.

In Pregnancy and Lactation. The highest calcium requirement would appear to occur during lactation, since 1 litre of human milk contains some 300 mg. of calcium. Even here if any bone disease occurs it is osteomalacia, which responds to vitamin D but not to extra calcium.^{50, 53} It seems clear that most women throughout the world are in strong negative balance for calcium during pregnancy and/or lactation. It seems certain that, like dairy cattle²⁰, they can draw on their calcium stores during lactation and replenish them afterwards. Hegsted³⁴ points out that there is no reason to believe this to be bad or unphysiological. In dairy cattle the losses are far larger in proportion yet calcium supplements are not required.

Holemans and Lambrechts and co-workers in the Belgian Congo⁴⁰ however, made an important investigation into the calcium balance of African mothers, who were suckling their children of 8 to 24 months of age. Their studies appear to have been performed with all due care, and each balance period was of 10-day duration. Five mothers were studied; their mean body weight was 43 kg. and they ate their own normal diet which included a mean calcium intake of 440 mg. per day. The mean faecal calcium was 300 mg., calcium in

urine 107.5 mg., and in milk 86 mg. per day (it must be presumed that the calcium loss via the milk would have been far greater had mothers been studied earlier in their lactation).*

This indicates a mean negative balance of 47.5 mg. per day. The point is that in these mothers there is no time *between* pregnancies and lactations for replenishment of calcium stores to occur, since one baby follows another throughout their whole fruitful life-period. Nevertheless no skeletal disorder has been described in these African women.

It appears from this and earlier observations in other parts of the world (Liu and co-workers in China⁴⁴; Toverud and Toverud in Norway⁷⁶; Adair *et al.*²; Macy and Hunscher⁵¹; and Oberst and Plass⁶⁵ in America), that pregnant and nursing mothers are not usually able to compensate for their excessive loss of calcium (to the foetus or in the milk) by increasing their intestinal absorption of calcium (reducing the faecal calcium). The "endogenous factor" of Nicolaysen does not seem to operate in these circumstances. Liu's conclusions⁴⁴ cannot really be improved upon today: namely that the calcium requirement in pregnancy and lactation is variable, conditioned by previous skeletal stores, previous dietary customs and the availability of vitamin D. One must conclude then, that while there is no real case to be made-out for giving extra calcium to pregnant or lactating women whose circumstances are good, yet women in the poorer parts of the world, who subsist on a low-calcium intake and suffer continuous calcium loss through childbearing, might well benefit from such a supplement. Even this has not been proved from the clinical point of view.

Excessive Intake. An excessive calcium intake, in the form of milk, together with absorbable alkalis in a patient with peptic ulcer may lead to the "milk alkali syndrome", characterized mainly by hypercalcaemia and chronic renal insufficiency.¹⁵ It is likely that the alkali is the more important aetiological agent, since in some cases of this syndrome it is the only one.⁶⁸

A high intake of calcium probably plays some part in renal stone formation, but in those patients with hypercalciuria, a reduction in calcium intake has a disappointingly small effect on their urinary excretion.³⁸ A high calcium and magnesium intake may be goitrogenic in the presence of borderline iodine deficiency (see Chapter 27).

Richards and Grieg⁶⁷ observed an impairment of reproductive capacity in female mice which had been fed with a calcium carbon-

* The calcium content of Bantu breast milk has been shown to be just the same as British or American milk, some 29 mg. per 100 ml.⁸⁴

ate supplement of the order of 1 per cent of their total food intake. The possibility that habituation to a low intake of calcium may offer some protection against future deprivation and the decalcification of old age has already been discussed.

Altogether, therefore, there would appear to be sufficient grounds for advising against an intake of calcium as high as that usually recommended. It is a sign of the times that the very first "Symposium on the Effects of High Calcium Intakes" has recently been held.⁷⁵

Calcium Deficiency Disease—Does it Exist?

It is difficult to prove that calcium lack *per se* is ever the cause of decalcification in man. The difficulty is two-fold; first that of obtaining "pure" cases, in which vitamin D, vitamin C, protein and calorie deficiency, disease, endocrine disorder, steatorrhœa and renal disease can be ruled out; and secondly that of the length of time which would be required for radiological demonstration of decalcification. Imagine⁵² a man with 1,000 g. of skeletal calcium who subsists on a daily intake of 200 mg. of calcium and has a consistently negative balance of 50 mg. per day. He would lose 16 g. per year, and it would take at least 17 years before ordinary X-ray examination would reveal evidence of demineralization (30 per cent loss). This question is, of course closely related to the problem of adaptation to low-calcium intakes. Obviously there must be some lower limit of calcium intake below which an individual will fail to maintain balance, but this would be expected to vary in different people, (the "good and poor absorbers" of McCance), may vary with the length of time allowed for adaptation, and might possibly eventually be very low indeed, so that no diet except virtual starvation could conceivably produce it.

Even the type of disorder which would be produced is uncertain. Malm assumes it would be "osteomalacia", but pure experimental calcium deficiency in rats produces osteoporosis (bone matrix deficiency) rather than osteomalacia (osteoid excess—defective mineralization). Albright⁴ believes that excessive calcium loss will produce osteomalacia (in idiopathic hypercalciuria and in the renal tubular acidosis syndrome)—but this cannot be accepted unconditionally.

Nordin^{61, 62, 63} and Whedon and his colleagues³³ believe that calcium deficiency causes osteoporosis by way of defective intake, defective absorption or increased loss (hypercalciuria). Both workers, using isotopic calcium methods, claim that there is no decrease in calcium accretion rate (i.e. bone anabolism) in osteoporosis, which

was believed to be the essential lesion on the Albright theory of defective bone matrix formation. Both claim improvement in balance studies from additional calcium alone. This thesis has yet to be proved. From the clinical point of view most authorities have not been impressed with the effects of calcium supplementation as a form of therapy.

Walker⁸¹ has carefully analysed the evidence that calcium lack is a cause of rickets. He concludes that among people whose calcium intake has been drastically reduced (as in wartime) rickets did not increase; in populations where the calcium intake is habitually low, but where there is sufficient exposure to sunlight, rickets or osteomalacia is not seen; finally that the ingestion of calcium salts has never been shown to have any beneficial effect in the prophylaxis or treatment of rickets. Our own data from Cape Town, based on an assessment of the calcium intake of rachitic children and a non-rachitic control group, is in agreement with the conclusion that this factor is of little importance.¹⁶

Conclusions

In this section I shall attempt to be dogmatic, though realizing full well that making a statement *ex cathedra* renders it no less fallacious.

(1) Rickets is common in many sunny parts of the world among less enlightened communities, and the basic reason for this is that the young children are kept out of the light.

(2) Rickets is not a feature of kwashiorkor, although under-nutrition in general limits growth rate while overnutrition may increase it.

(3) All grades of sensitivity of children to vitamin D may be encountered—in some cases quite moderate amounts of vitamin D will lead to hypercalcaemia.

(4) Any type of malabsorption which produces steatorrhoea may produce osteomalacia, and probably some degree of secondary hyperparathyroidism

(5) The aetiology of the varieties of generalized osteoporosis remains uncertain. Deficiencies of vitamin C, calcium and protein have not been proved to be causative.

(6) There is no good evidence that either protein deficiency or calcium deficiency produces *per se* any bone disease in man, although a rarefaction, other than osteomalacia, is undoubtedly seen under certain conditions of malnutrition and undernutrition.

(7) The lower limit of requirement of calcium in adults, in children,

and in pregnant and lactating women is unknown; it is very much lower than the level of intake usually advised. Adaptation to low calcium intake is the rule. *There appears to be no good evidence in favour of supplementing the calcium in the diet of any normal, healthy person in any circumstances whatever.* Habituation to a low-calcium intake may even be of value to the organism.

There is probably equally little factual evidence in favour of the use of additional oral calcium in any disease state whatever (with the single exception of acute states of recovery from decalcification, e.g. post-operative hyperparathyroid bone disease). If any people might benefit from extra calcium it would be those who live in areas of chronic undernutrition, and even in them the benefit is problematical.

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CHAPTER 26

NUTRITION IN OLD AGE

by
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Owing to a misunderstanding this chapter covers only trends in the nutrition of the aged and is therefore not comparable with similar chapters reviewing general trends in clinical nutrition as published in the French, Spanish, Portuguese and Russian languages. Nevertheless it covers a field not otherwise covered in the monograph and has a large bibliography in German.—EDITOR.

For years the problem of nutrition in old age has been increasing in importance. One of the reasons for this is the shift in the age groups of the population that is observable in all civilized countries. Since the turn of the century the average human expectation of life has risen by about 15 years. Men do not in fact live to be older, but more men live to old age. In the Federal German Republic, for example, between 1880 and 1952 the fraction of those over 65 years of age had risen from 4·8 per cent to 9·3 per cent; according to calculations it will have reached about 13·5 per cent by 1972.^{39, 41, 43, 58, 63}

Another reason is the increasing knowledge of the biological processes associated with ageing and the relations between ageing and disease.¹⁰ Here it has been shown that nutrition too, in both quantitative and qualitative respects, plays an important role. But this general conclusion must not delude us into thinking that in this field there are not still very considerable gaps remaining in our knowledge.

In this connection too, we must bear in mind that age in years certainly does not coincide with biological age. Ageing is a fluid and cumulative process in operation from birth on⁴² which in later years may be abruptly accelerated.¹³ We say a person is ageing when this becomes apparent. Up to the present there is no test of biological age. We judge, therefore, from the overall impression and from external indications which point to degenerative symptoms and cause a person to appear old.⁴⁴ Doubtless, impressions may be deceptive and it is certain that symptoms of old age may appear at very different periods of life.

The hope that diet or medicine may bring about the rejuvenation of the old will not be fulfilled. Once biological old age has been reached, it is irreversible. The object of our endeavours can, therefore, only be to slow down the ageing process, to relieve deficiency conditions and, by well-considered measures, to facilitate recovery from illness.

For the attainment of these goals it is agreed that in old age suitable nourishment plays an important part. It is estimated that, in the case of two-thirds of all old people, nutrition does not meet the desirable requirements.⁶²

In the following account only problems of topical interest or practical importance concerning nutrition in old age can be briefly outlined. At the request of the editor, I shall restrict myself mainly to literature in the German language and to my own experiences.

Dietary Requirements

If we review the recommendations for human nutrition, we are struck by the fact that relatively little consideration is given to figures for the requirements of the old. Often, moreover, nothing reliable is known. The preparation of such requirement standards is, of course, attended by special difficulties: in the case of old people there are considerable variations in living conditions and the capacity for work. Not infrequently the boundaries between the physiological symptoms of old age and pathological conditions in old age are blurred. In its particular requirements and effects the nutritional prophylaxis of the so-called diseases of old age is certainly not fully understood as yet. But, without any doubt, all nutritional physiologists and doctors agree today that in old age the average nutritional requirement deviates from that of the middle and younger age groups in many respects. In particular, there are the following results^{15, 18, 54}

Caloric Requirements. With advancing years the basic metabolic rate drops, the metabolically active muscle mass decreases, bodily activity declines. The result of this is a decrease in caloric requirements. According to the recommendation of the Deutsche Gesellschaft für Ernährung¹⁵ this is, for men of 65 not engaged in heavy physical work, approximately 2,150 cal./day and for women under similar conditions approximately 2,000 cal./day. The recommendations of FAO¹⁸ are based on the standard values for 25-year-old men (3,200 cal./day) and for women of the same age (2,300 cal./day) whose physical activities are light, at an average annual temperature of 10° C. The following deviations from these standards are recommended for the later decades of life (see Table 1).

TABLE 1

<i>Age in Years</i>	<i>Percentage of Standard Value</i>
20-30	100
30-40	97
40-50	94
50-60	86.5
60-70	79
Over 70	69

According to this, the recommendations for 65-year-old men (2,500 cal./day) and 65-year-old women (1,800 cal./day) give somewhat divergent values. From nutrition surveys of the over 70-year olds, we arrived at an average caloric intake of 2,300 cal./day for men and 1,900 cal./day for women.²⁹ As a general coefficient, therefore, the requirement may be estimated at about 2,000 cal./day, for old men rather higher and for old women rather lower. However, there may be considerable individual fluctuations, depending primarily on the degree of physical activity still possible. Corresponding additions and deductions are then necessary. Climate must also be considered in fixing caloric requirements. According to the recommendations of the FAO Committee additions or deductions of 3-5 per cent are necessary for deviations of 10° C. at any given time from the reference temperature (10° C.).

Protein Requirements. From the nutritional-physiological standpoint there is no convincing evidence proving the need for an intake of protein greater than in the middle age groups. The opinion of some that old people utilize protein enterally less well can be as little endorsed as the supposition that old people have a higher endogenous consumption of protein. Schulze's⁵⁵ investigations with 60-92-year-old test subjects showed that the enteral utilization of proteins in different test diets was just as good as in the case of younger controls. The physiological protein minimum also was, in the same way, fixed at 0.5 g./kg. Therefore, for old people too, the optimal protein requirement could be established at 1.0 g./kg. (about 65-70 g./day), as is suggested for adults of the middle age groups to maintain a state of well-being and the capacity for work.^{15, 35.}

But from the medical standpoint, it has been recommended again and again that, for old people, the daily intake of protein should be higher, namely 1.2 to 1.5 g./kg./day. With the restricted intake of food in old age there is greater risk of a failure to reach the

optimal protein level; it is also assumed that in old people the potential protein reserves of the organism are less, so that, when heavy demands are made upon them, a sudden lack of protein can occur. Finally, a higher intake of protein is desirable in old age on account of the higher specific dynamic effect, as it checks the tendency, common in old people, to accumulate fat.⁴³

The intake of high-class protein foodstuffs is important, but the question of how large the animal fraction of the dietary protein should be for old people is difficult to answer. Sufficiently reliable values for requirements can hardly be quoted. In the recommendations of the Deutsche Gesellschaft für Ernährung,¹⁵ 0.4 g./kg. (= round about 30 g./day) is given as desirable for normal persons. It is not known that old people need more, but when it is seen how much more unfavourable the course of, for example, diseases of the liver is for the average old person than for younger⁷ ones, one is rather in favour of higher values (about half the daily protein intake).

Intake of Fat. According to the American recommendations, which agree more or less with the German ones, for normal persons not engaged in heavy work, not more than 25–30 per cent. of the total calories should consist of fat calories. Since old people are especially prone to degenerative vascular diseases, in old age the consumption particularly of fat should be restricted. Thus it is recommended⁴³ that in old age the quota of fat should at the most provide 20–25 per cent. of the total calories (about 45–60 g./day). This includes “visible” fat (on bread, etc. and cooking fat) and “invisible” fat. In the case of already existing vascular disorders with hyperlipidaemia, or in digestive disorders, such a rigorous restriction of fat may be necessary and expedient. But this restriction should relate only to definite pathological states occurring in old age. The general recommendation that in old age fat should provide only 20 per cent. of total calories, does not seem to me to be sufficiently substantiated yet and, moreover, from the practical standpoint, it is difficult to carry out. For the time being I consider it sufficient to avoid exceeding 30 per cent.

Part of the fat should consist of varieties that are rich in highly unsaturated fatty acids, since these are supposed to have a favourable influence with respect to the development of atherosclerosis and can lower the blood fat level.^{5, 8, 24, 33, 60} According to American recommendations, these fatty acids should constitute about 1 per cent. of the fat calories. The addition of oils rich in polyene acid to the diet of the old should, therefore, be considered.

Carbohydrate Intake. The level of the necessary intake of carbohydrate is determined for old people too by the difference between the requisite total of calories and the quantity of protein and fat calories, which has already been established. The carbohydrate requirement, therefore, constitutes approximately 55–60 per cent. of the necessary total calories (about 250 g./day).

Vitamins. The provision of an adequate supply of *vitamins* forms a special bottle-neck in the diet of the old. The vitamin requirements of old people are supposed to be unconditionally higher than those of adults of the middle age groups.^{6, 49} Various reasons for this are brought forward: deterioration of enteral resorption, increased endogenous requirements in cell metabolism and the special state of the bacterial intestinal flora in old age.⁶⁵ Of course, nothing certain is known about actual vitamin requirements in old age. Mellinghoff⁴³ recommends double the usual quotas in old age. In our nutrition surveys of old people, we found considerable shortfall in relation to recommended allowances; above all inadequate amounts of vitamin A (recommended: 5,000 I.U./day of vitamin A and carotene, of which 1,000 I.U. are vitamin A), vitamin B1 (recommended: 1.7 mg./day) and vitamin C (recommended: 75 mg./day).

Minerals. Calcium deficiency, relative to recommended allowances, is comparatively frequent even among the average population. Since an appreciable deficit can produce skeletal changes,⁴³ this must have a particularly unfavourable effect in view of the osteoporosis of old age, which is physiologically already present. In old age the ensuring of an adequate calcium intake should have special consideration because of reduced food intake, the possibility of increased difficulty in enteral resorption and probably impaired utilization. The desirable intake for normal people is given as 1.0 g./day.¹⁵ In old age this amount should not on any account be reduced. The desirable proportion of calcium to phosphorus (1 : 1 to 1 : 2) is usually attained.

Because of the proneness of the old to hypertension, water retention and obesity, it is advisable in the case of old persons to restrict the supply of sodium chloride. According to Mellinghoff's⁴³ recommendations, not more than 5–7 g./day is permissible.

Trace Elements. Compared with that of younger persons, the iron resorption of old persons is, according to Rechenberger's investigations,¹⁰ distinctly reduced. The serum iron level drops with advancing age,⁵² anæmias are not infrequent in old people and are, for the most part, iron deficiency anæmias. In the case of old persons, the desirable level of the daily intake of iron, 12 mg./day should be secured;

our own experiences show that this is frequently not done. A sufficient supply of vitamin C to enhance resorption might also be considered.

Choice of Food

Practical suggestions concerning the suitable choice of food for old people have come from various sources.^{3, 14, 19, 23, 25, 31, 34, 43, 62} As a general rule, the diet of the old should be simple, light, easily digested and well-tolerated. Heupke²⁵ once gathered information about the life of 30 men and women, who had reached the age of 100–107 years. They belonged to the rural population and were active until they had attained advanced old age. Their diet was simple and consisted of bread, meat, abundant milk and yoghurt, plentiful vegetables and fruit. This selection is in accord with principles that are recommended today for old people.

It is weight primarily that must decide the overall *quantity of food*. Old persons who are considerably underweight need, as a rule, a body-building diet correctly adjusted with regard to quantity (see below). However, in old age, there is usually a tendency to corpulence, more commonly in women than in men. In that case a reducing diet (see below) may be indicated. While it is less a matter for concern if the weight of young persons exceeds the desirable limits, this should not be allowed in older people over 40. In the selection of food particular attention should be given to *protein-containing nutrients*, especially to those with high-grade protein. In this respect milk should have first place in the diet of the old. It is almost indispensable in ensuring the necessary requirement of calcium in old age. Milk is easily digested and well-tolerated and can be taken and served in many different ways. A daily quota of half a litre is recommended. That contains 17 g. of first-class protein. The remainder of the requisite daily amount of animal protein (about 22 g.) can be derived from meat, fish, poultry or white cheese (average serving).

In order to ensure that intake of *fat* is restricted, special attention must be given to “invisible” as distinct from “visible” fat. Therefore, when shopping, care must be taken to choose suitable food-stuffs. This applies above all to protein-containing foods with high-fat content. The preference of old persons should be for skim-milk, skim-milk cheese, lean meat, fish and poultry, also game. Sausage, which in this country contains at least 50 per cent. of fat, should be avoided as far as possible. Eggs need not be excluded from the diet of the old.⁴³ However, since the lipid content of an egg is about 6 g. not more than one per day should be eaten. The quantity of visible

fat should be restricted and not exceed 30–40 g./day. First class fats, which are rich in fat-soluble vitamins and polyene acids are to be recommended. Margarine should be vitaminized.

Old people should exercise restraint in the enjoyment of foodstuffs with a concentrated *sugar* content (sweets, confectionary, chocolate). Sugar as sweetening in coffee or tea is permissible in small quantities, not over 30 g./day.⁴³ Other foodstuffs, however, that are rich in carbohydrate should also be taken in small quantities (pastry, puddings, potatoes, bread).²³ The quota of potatoes should not exceed 300 g./day.

To ensure an adequate intake of *vitamins* and *minerals*, brown bread is to be preferred to white and fancy breads. Many old persons digest this without trouble. However, it must be noted that bread made with high-extraction flour (whole-meal bread) is less well utilized and prevents the resorption of vitamins, and, most important, of calcium also (as a result of the phytin content of the bread).³⁷ Fruit (about 300 g./day) and vegetables (about 300 g./day) including some raw vegetables should be generously provided.

Many old persons suffer from constipation. Hence the diet of the old should incorporate sufficient *roughage*—as far as this is tolerated. A general restriction of *fluid* intake is certainly not called for, on the contrary about 2 litres of fluid should be taken daily. Fruit and vegetable juices, milk and milk shakes, are specially to be recommended. Coffee and tea also are permissible if they are not indulged in too late in the day. There is no contra-indication to *alcoholic* drinks, so popular with old men, provided they are taken only in moderate quantities.

The diet of the old should be light, not over-burdening the digestive organs, easily digested and well-tolerated. Suitable preparation of the foodstuffs is necessary to satisfy these requirements. Good digestibility is by no means the same as toleration.²² Good digestibility relates to the enzymic decomposition of the foods in the digestive tract. It is often asserted that enzymic deficiency is a characteristic of old age.^{5, 43} This general statement has not been adequately substantiated, and it is moreover, difficult to prove systematically. The parotid amylase appears to change with age, but obviously not the production of acid by the stomach. The occurrence of gastric anacidity shows no greater frequency in the higher age groups.¹⁰ Toleration is determined partly by the physical qualities of the foodstuffs (quantity, hardness, ease with which it may be cut up, toughness, water content, ability to be emulsified, temperature) and, on the other hand, depends to a considerable extent on personal

feelings, tastes and feeding habits.²⁶ If so-called digestive troubles are not responsible for lack of tolerance, there are usually pathological states present, to which attention must be given.

As regards the choice of meat, it is not the cut (apart from its fat content) that decides its digestibility and toleration, as much as its quality and tenderness, and also its culinary preparation. It is somewhat the same in the case of vegetables. Here, too, it is the freshness, the tenderness of the fibres, the size of the pieces and the mode of preparation rather than the kind of vegetable that is of importance.

Very fatty dishes, which old persons should avoid in any case because of their high-fat content, make specially heavy demands on digestion and powers of toleration. Therefore, meat boiled or grilled, for example, is more desirable than fried in fat or crumbed. Vegetables should be steamed without fat. To increase the value of cooked vegetables, finely shredded raw vegetables should be added to them and, to improve the flavour, a dab of butter should be added *after* they are done.

Seasoning is not only permissible in the diet of the old, but is also necessary, to enhance palatability and toleration. We found that many old persons both like and tolerate piquant seasonings such as pepper and paprika, if used in moderation.

In place of *soups*, which contain unnecessary quantities of fat, fresh salad should be served before the main meals, particularly before the midday meal. Bread should be stale. Foods causing flatulence are to be avoided.

It is not my concern to go into further details on this subject. Excellent suggestions on questions of digestibility and toleration are to be found in the unjustly forgotten book of Noorden and Salomon⁵⁰ and also in that of Hoesslin²⁶ as well as in the relevant nutrition textbooks and handbooks.^{7, 20, 22, 37, 61, 64}

Sociological and Psychological Aspects

Even though there are well-founded ideas about the pre-requisites of a suitable diet for the old and every effort is made to apply them, the results are often disappointingly meagre. This has been the experience of every dietary therapist, even where insight and co-operation would most have been expected. Dietary histories carried out in our hospital on diabetics, who had repeatedly been given instructions, showed that hardly 20 per cent of them had followed the doctor's recommendations satisfactorily. Eighty per cent adhered to them either only fairly well or not at all.⁵¹ Dietetic recommenda-

tions can only be followed permanently if they are adapted to the sociological and psychological background of the individual. That is more difficult with old people, who also constitute a large proportion of diabetics, than with younger ones.

Age and Activity. The recommendation of a caloric restriction to about 2,000 cal./day applies to the still relatively active old person, who does not perform any physical work worth mentioning. That is the case with many persons over 65. Nevertheless, in 1950, 25 per cent of the old men and 10 per cent of the old women over 65 in the Federal German Republic still had earning capacity. Even the aged are still capable of remarkable achievements. It is notable among old persons with earning capacity, that professional people and farmers preponderate.

Gsell²¹ discovered remarkable differences between urban and rural populations. In towns, the consumption of calories (on the average 1,900 cal./day) found by him for the 59–90 year-olds, agreed with standard estimates. On the other hand, he found substantially higher values (on the average 2,750 cal./day) for old people in rural populations. There even 74–79-year-old women were still active. The caloric intake of old persons in rural populations, if these still worked, corresponded to that which would also be estimated for younger adults under the same conditions. Caloric intakes were even found such as are characteristic for manual labourers (3,800 cal./day).

Kapp and Fischer³² found very different and quite divergent values in the case of 424 inmates of homes for the aged. The average caloric intake amounted to 1,700 cal./day. Very careful and detailed enquiries in the case of 23 old persons, half of whom were bedridden, produced the surprisingly low value of 977 cal./day. In these people, however, there were no indications either of anæmia or hypoproteinæmia or of symptoms of hypovitaminoses. Obviously their metabolism had become adjusted to the level of *vita minima*.

In any case, with respect to old persons, schematic conclusions about the daily caloric intake are not justified. It is possible that the theoretical calculation of caloric requirements from basic metabolic tables (e.g. those of Boothby-Berkson) may also lead to fallacies. Attention was drawn to this by Gsell and also by Kapp and Fischer. The former found values were too low, the latter too high. Years ago even Bürger drew attention to the fact that basic metabolism is largely dependant on muscle mass of which the creatine index is a measure.^{10, 53} Likewise, in requirement estimates that are based on body weight, too high values are given for adipose old persons.

Feeding Habits of the Old. It is frequently the exact knowledge of feeding habits that uncovers the actual dietary errors and thus indicates suitable ways of introducing appropriate modifications in nutrition. In the case of old persons, such specially adapted dietary adjustments are the most effective. Dietary histories of a suitable and practical kind^{28, 69} are of use for this purpose.

Such investigations^{4, 17, 21, 27, 30, 32} showed that old persons prefer a concentrated diet, rich in protein and fat. On the whole, they like milk, meat, fruit and vegetables.⁴ Only 5 per cent of Kapp and Fischer's old people ate no vegetables.³² Choice of bread is not governed at all by its digestibility, but is rather a matter of habit. Two-thirds of the old persons could tolerate brown bread (85 per cent extraction). Gsell reports that while in the town of Basel 51 per cent of the old people questioned did not eat brown bread, only 16 per cent did not in the rural population of old people in Calancatal (Switzerland). The preference for fat is evidently general, in this country primarily for butter, while margarine, even if it had been eaten at an earlier age, was frequently refused, because of its taste but probably also because of social standards. Opinion is divided as regards preference for sweet foods.^{1, 32} According to our own experiences old women are certainly inclined to eat sweet things. In the case of old men we found rather a preference for alcoholic drinks. There was a reluctance to give up soups and sauces. Coffee is extraordinarily popular.

But eating habits show considerable individual differences, determined by nationality, tastes, social standards and also by knowledge of cooking and of the different commodities available.

Diet and Income of Old Persons. About 70 per cent of old people over 65 live on investments, pensions or relief.³⁹ The income level may be extremely modest. Special difficulties may arise if outlay on food has to be cut down. Yet a desirable diet for the old means increased expenditure, since low-fat protein foods and also fruit and vegetables are expensive. But, even with little expenditure, wise buying and a knowledge of available commodities will make a suitable diet possible. Old people in particular are not always knowledgeable in these matters. But we find also, that even old people of small means will expend considerable amounts on their food and prefer expensive foods to cheaper ones.²¹

Diet and the Household of Old Persons. Whether dietary recommendations are followed depends on those who are responsible for the preparation of the food. Consultation with the relatives of old persons is, therefore, often a prerequisite for a real change in diet.

The inclination of old people themselves for this change is frequently not enthusiastic. Understanding is often hampered in old age by impaired powers of concentration and judgement. Special difficulties arise in the case of solitary old people, particularly in the case of old men: in Germany about 10 per cent of men over 60 live alone, 32 per cent at this age are either unmarried, widowers or divorced. With increasing years these figures grow still more unfavourable.³⁹ Here there is a special problem for the consideration of nutritionists, in the solution of which domestic and social welfare workers could co-operate.²³

The Communal Care of the Aged. It has become more and more manifest that the food provided in homes for the aged does not reach the desirable protein optimum: the amount of fat is too high, the fruit and vegetables provided are unsatisfactory in respect to quantity and preparation.^{17, 27, 30, 32} Our personal experience bears this out. This being so, it should be the business of the responsible doctor of the institution to investigate the diet and endeavour to improve it.

Similar conditions obtain in hospitals, in which there are increasing numbers of old patients. Particularly in special hospitals for internal diseases, the ratio of old patients today is considerable. In 1958 it amounted to 26 per cent in our hospital. Mellinghoff⁴⁵ reported that in his hospital it was 39 per cent. Störmer's⁶² figures were yet more unfavourable. Surveys in representative institutions for the sick in the Federal German Republic⁹ established the following values for the daily hospital diet: calories, 2,800; proteins, 12 per cent; fat, 40 per cent; carbohydrate, 48 per cent. We must bear in mind here that most of the patients were bedridden. The Institut für Ernährungsberatung und Diätetik in our hospital has, therefore, worked out sample dietary tables for two large hospitals, which involved only a small increase in expenditure and met with the approval of both patients and staff.⁷¹

Psychological Problems of Old Age. No one who is concerned with questions arising from the care of the aged can afford to ignore problems connected with the psychology of old people, if their efforts are to be crowned with success. People are fond of stressing this, yet it is seldom acted upon. Moreover, there often exist quite wrong viewpoints, which only look at the personality of old persons from the angle of symptoms of decay and degeneration. Quite a number of excellent works and articles deal with this subject.^{56, 57, 66, 67, 68, 70} This is not the place to consider this in detail: we shall only include some points of interest that are relevant to our subject.

Bodily pleasures (food, luxuries) may play, for example, an important part in the life of the old person. This has been bluntly referred to as a return to the oral-anal stage, an exaggeration which applies only in extreme cases. Nevertheless, old people do appear to have a preference for refined foods. For other old people these things are of no importance. Their main interests lie in quite other directions: concern for their family, for their possessions, preoccupation with religious ideas. They are indifferent about other subjects: these do not arouse any interest in them. This makes a modification of their diet specially difficult.

It has been confirmed repeatedly that old persons in institutions, where they are relieved of all personal anxieties and responsibilities, keep on complaining, mainly about food, although its tastiness and wholesomeness do not justify complaint. A recurrent, and often not unjustified, complaint is that the food is not varied enough. It is interesting and surprising that in a questionnaire in one of the larger homes for the aged as to which dishes should certainly *not* be taken off the menu, the answers included those which are considered difficult to digest and badly tolerated. Further enquiries about eating habits in their parents' home showed that they had been used to these dishes from their youth.

A question of importance concerning the diet and the dietary training of the old is to what extent we should endeavour to influence old people. We must always bear in mind the advantages and disadvantages involved. There are not always advantages only. The old person, too, is an individual, whose psychological idiosyncrasies should be respected, even if he is physically handicapped. Sudden changes in diet are not recommended, because these may be associated with emotional strain, to which old people are more susceptible.

Invalid Diet

Nutritional therapy for diseases in old age should be governed by essentially the same principles that apply to invalid diet in other cases. They depend on the type of disease requiring dietary treatment. It is not my concern here to discuss these principles at length: they have been described in detail elsewhere. I should, however, like to refer to some few topical points which the dietary therapist should consider with respect to old persons.

The general principles determining the diet of the old, which have been described earlier, form the basis of all dietary therapy for the old. Therapeutically necessary modifications must be in accordance with them. Mellinghoff⁴³ emphasized above all that in old age dietary

therapy must in the first place take into account quantitative considerations. The commonest error in the dietetic treatment of old people is inadequate consideration of their bodily requirements. Insufficient food can have a really deleterious effect on old persons. If the intake of necessary nutrients is inadequate, recovery from illness is slower and more difficult, complications are more frequent, convalescence is prolonged. Above all, in chronic conditions, which indeed are especially frequent in old age, a high-class diet is the most important dietary requirement. In certain circumstances the usually recommended requirements, chiefly of protein, vitamins and minerals must be considerably exceeded. Of course, the initial nutritional state is what must decide dietary treatment.^{45, 46, 47, 48}

Old persons whose nutritional status is poor are in urgent need of a "body-building diet", in order to acquire as efficient powers of defence and resistance as possible. But the increase in food intake should not be abrupt but slow and gradual. Since the utilization of glucose in old age becomes increasingly poor,² fructose, the utilization of which remains unimpaired, should be introduced into the dietary schedule. If appetite is poor, or if there are digestive troubles, amino-acid hydrolysates can be given orally or parenterally to contribute to the protein requirement. To ensure an increased caloric intake without too great an increase in the volume of food, the body-building diet must include a more generous quota of fat, approximately up to double the quoted standards. Here, too, use can be made of dietetic food products which contain fat in an acceptable form as concentrates. Preparations rich in polyene acid are especially to be recommended. In addition increased quantities of fat encourage glycogen synthesis, nitrogen and calcium retention.³⁶ It goes without saying that a body-building diet must be rich in vitamins.

Obese people must frequently follow a "reducing diet" as the treatment of various diseases (hypertension, diabetes mellitus, cardiac insufficiency, degenerative skeletal changes). Here, too, the principle must be applied that sudden dietary modifications or drastic restrictions are not suitable for old people. This holds particularly for fasting cures. The daily intake of calories should on no account drop below 1,200 cal./day. Protein, vitamins and mineral substances should not, as far as possible, be restricted; it is mainly carbohydrate and fat that should be cut down.

The *diabetic diet* in itself accords very closely with the general principles of diet in old age. It should be rich in protein and low in fat and carbohydrate. Obesity is particularly frequent among old diabetics, especially among women. In that case regulation of the

metabolic state is not sufficient but, in addition, a reducing diet must be followed. However, it is not desirable to restrict the carbohydrate intake too drastically. 150 g./day should be the lower limit. If this amount is not tolerated, fructose can be administered here also, but in limited quantities (about 40 g./day), without fear of any significant deterioration in the metabolic condition. The metabolic pathway of fructose is not the same as that of glucose. Its utilization is (probably partially) independent of insulin.^{38, 40} Bürger^{11, 12} reports excellent successes in the treatment of diabetic gangrene, which occurs predominantly in old age, with a diet very rich in carbohydrate (400–600 g./day), which in the case of many old diabetics made amputation unnecessary. On the other hand, v. Eck¹⁶ with a diet extremely low in fat (about 20 g./day) could produce a favourable effect on the dreaded diabetic retinopathy, and even cause it to regress. Of course, the diet must remain rigorously low in fat for a long period.

A dietary formula designated as the *antisclerosis diet* is becoming more and more widespread. It is meagre, low in fat, rich in polyene acid and vitamins A, E and B₆. Germ oils with a high content of highly unsaturated fatty acids are introduced into this diet.^{24, 43, 59} It is not the place here to discuss the pros and cons of such dietary formulæ. They are chiefly indicated in the case of atherosclerotic vascular disorders with established hyperlipidæmia.⁵⁹

A *diet low in sodium chloride* must often be prescribed for old people with hypertension, œdematous cardiac insufficiency and obesity. Strict NaCl-restriction is particularly difficult to achieve in the case of old persons. Moreover, it should only be carried out in urgent and exceptional cases, since anorexia is not infrequently the result and the food intake may very easily become inadequate.⁴³ A restriction to 3.0 g. NaCl/day may be attained without very much difficulty.

Reference should be made here to Holtmeyer's⁷² recent work. The customary calculation of the NaCl content of foodstuffs may lead to fallacies. Holtmeyer has shown that, with respect to water retention, the effects of the ions Na⁺ and Cl⁻ must be considered separately. In foodstuffs they are not by any means present in chemically equivalent quantities. Foodstuffs that are low in Cl⁻ are still often regarded as low in NaCl. They can, however, contain large amounts of Na⁺. But foodstuffs that are high in Na⁺ and low in Cl⁻ may, with foodstuffs that are high in Cl⁻ but low in Na⁺, have a greater effect on water retention. It is, therefore, more useful to analyse and group dietary foods according to chemical units of mea-

sure (milliequivalent = mEq.). Above all, this has the advantage of making a diet that is low in Na^+ and Cl^- more varied. Holtmeyer gives many recipes on these lines. Moreover, especially in the case of old persons great variety is desirable.

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CHAPTER 27

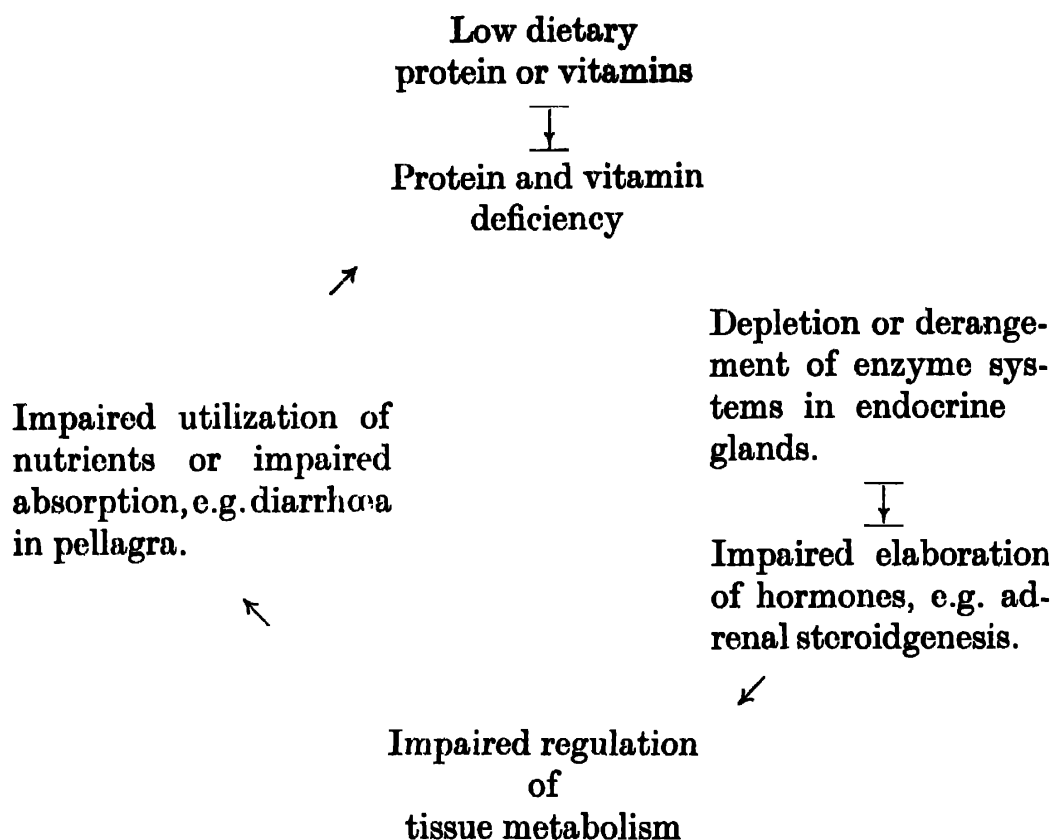
THE EFFECTS OF ALTERED NUTRITION ON THE FUNCTION OF THE ENDOCRINE GLANDS

by

A. O. LURIE and W. P. U. JACKSON

WHILE many of the effects of malnutrition on various organs are well known, comparatively little attention has been paid to the endocrine glands. Possibly the subtle signs of adrenal or pituitary deficiency are overshadowed by dramatic manifestations such as skin lesions, dementia, peripheral neuritis and œdema. The volume of literature and work lavished on iodine-deficiency goitre is an example of the attention which is paid to the obvious.

Nutrition plays a vital role in the function of the endocrine glands. The pathogenesis of the structural and functional changes which are produced in these glands by protein and vitamin deficiencies is unknown. What is known, however, is that malnutrition may alter tissue enzyme systems both quantitatively and qualitatively. This has been demonstrated and its significance discussed by Waterlow.⁷⁷ Alteration and depletion of enzyme systems may well be the cause of endocrine gland dysfunction and failure. Recent research on the biosynthesis of steroid hormones in the adrenal cortex has shown that vitamin B-containing co-enzymes, e.g. Triphosphopyridine nucleotide (TPN) are essential factors in this process.⁵⁶ Wettstein *et al.*⁷⁸ have found that the addition of nicotinamide or adenosine triphosphate (ATP) to beef adrenal gland homogenates greatly increases the production of aldosterone and other steroids. Our own experiments have shown that prolonged stimulation of the adrenal glands by adrenocorticotrophic hormone (ACTH) in some patients suffering from pellagra produces a marked diminution of urinary steroid output. These phenomena suggest that nicotinic acid and protein may be limiting factors in steroid biosynthesis. The effects that hormone lack or excess have on tissue metabolism are well known. Impaired tissue metabolism will in turn impair the utilization of nutrients. A vicious circle such as that referred to in Chapter 3, may thus be set up. It should be realized, however, that this is certainly an oversimplification of a highly complex and largely unknown sequence of events.



Suggested Scheme of the Manner in which Endocrine Glands may enter into the Vicious Circle Mechanism in Malnutrition
(See text.)

It is proposed to give an account of recent advances in this interesting field, with special emphasis on the practical implications that have emerged. Undernutrition, overnutrition and other varieties of malnutrition, acute or chronic, may each have different effects on the endocrine glands and they will therefore be considered separately where relevant.

The Sex Glands

Autopsy examinations on patients who suffered from chronic malnutrition have shown that the ovaries are small and atrophic, and the germinal follicles poorly matured. In the male, atrophic changes in the testes, decrease in size of the seminiferous tubules, focal fibrosis, and decrease in germinal epithelium have been found on histological study. Zubiran and Gomez-Mont⁸² believe that the testes of young patients typically show retrogressive changes of the type associated with senile involution.

Clinically, males may undergo a process which has been described

as "feminization". This is evidenced by testicular atrophy, loss of libido, infertility, loss of body hair with the appearance of a female type of escutcheon, prostatic atrophy and gynæcomastia. In the female, loss of libido and disturbance of menstrual function which varies from oligomenorrhœa and/or irregular menses to complete amenorrhœa are frequent.^{24, 32, 35, 68, 82}

Estimations of urinary œstrogens in patients suffering from chronic malnutrition have revealed low values⁸² and similar findings have been reported in patients suffering from anorexia nervosa.^{3, 49} In both conditions low levels of pituitary gonadotrophins were also found in the urine, and this is highly suggestive of primary failure of pituitary function.

A full review of the effects of malnutrition and vitamin deficiency on gonadal function in the animal kingdom has been reported by Lutwak-Mann.³⁹ In particular she found no evidence whatever that vitamin E plays any part in gonadal function in man.

Gynæcomastia. Gynæcomastia occurs not uncommonly in the African, and is usually assumed to be related to malnutrition, although there may be no overt indications of this. Trowell⁷² found an incidence of 5 per cent in "normal" African railway workers as compared to a 16 per 100,000 incidence in soldiers in the United States army.³³

The pathogenesis of gynæcomastia has always provided an intriguing problem. The suggestion that excessive circulating œstrogens are solely responsible is probably too facile. It is true that exogenously administered œstrogens can produce gynæcomastia; furthermore the "feminization" which may occur in states of malnutrition suggests œstrogenization. However, many other agents may cause growth of the male breast, including androgens, digitalis, adrenocortical extracts, desoxycorticosterone, the clinical states of thyrotoxicosis and certain varieties of testicular failure.

Gynæcomastia frequently occurs with malnutrition or disease of the liver. It has been postulated that the damaged liver in malnutrition fails to inactivate œstrogen, so that high circulating levels result. An excessive production of œstrogen is not implied. This hypothesis leaves unexplained the infrequency of gross liver dysfunction in malnutrition and, of greater importance, the fact that gynæcomastia characteristically appears *after* the initiation of cure by refeeding.⁵⁶

Summerskill *et al.*⁶⁶ have shown that gynæcomastia in cirrhotic patients occurs only when the liver disease is caused by chronic alcoholism. Similarly they found that a high incidence of chronic

malnutrition occurred only in patients whose cirrhosis had an alcoholic basis.

Early reports claimed that there was a considerable increase in urinary oestrogen excretion in patients suffering from liver disease. In some of these there was no evidence of gynæcomastia. Conversely, it was found that in some cases with cirrhosis and gynæcomastia, the level of urinary oestrogen was within the normal range. Recently Cameron,⁹ using a chemical method, claimed that urinary oestrogen output was normal in his cirrhotic patients. The high urinary oestrogen level, previously reported by others, was, he felt, due to the biological method of estimation. However, Bloomberg *et al.*,⁴ using the same chemical method, investigated African and white patients suffering from hepatic cirrhosis and came to the conclusion that there is an increase in urinary oestrogen in this disease. It is obvious that further work in this field is essential and it should be remembered that the chemical methods now in use measure only three of the known fractions of oestrogenic metabolites.

Atrophy of the testes is a common finding in both cirrhotic and malnourished patients, and this together with oestrogen excess has been considered as the cause of gynæcomastia. It has been suggested that an increased or normal amount of oestrogen has a greater potential "gynæcomastia-producing" action if there is a deficiency of male sex hormone. Spankus and Grant⁶¹ expressed their findings in terms of the ratio of oestrogen to androgen and claimed that this ratio was consistently high in patients suffering from gynæcomastia. This has been confirmed by others.^{5, 15, 25} On the other hand, the ratio was also found to be high in cirrhotics who had no gynæcomastia.⁵⁴

A further problem was presented by a consistently normal level of urinary oestrogens in "refeeding gynæcomastia".⁵⁶ Zubiran and Gomez-Mont⁸² claimed that patients who developed refeeding gynæcomastia had a considerable rise in urinary oestrogen before the onset of breast enlargement. By the time the gynæcomastia was well established, the urinary oestrogens had returned to normal. It is also known that gynæcomastia produced by exogenous oestrogen can persist for some time after stopping the hormone. Salter and his co-workers⁵⁶ commenced their investigations 3 months after the gynæcomastia was well established, so that their finding of normal urinary oestrogen levels is not surprising.

Lyons *et al.*⁴⁰ have shown that an intact pituitary gland is essential for the production of mammary duct growth in their experimental animals. Their work clearly suggests that there is no single mam-

motrophic factor. Growth of duct tissue appears to be the result of a number of hormones acting together on the breast. The factors responsible are mainly follicle stimulating hormone (FSH) which, with interstitial cell stimulating hormone (ICSH), stimulate the ovary to produce oestrogen, somatotrophic hormone (STH) (or growth hormone) and an adrenocortical steroid (in their experiments deoxycorticosterone acetate (DCA) was better than cortisone). In hypophysectomized male rats, it appears that duct growth can occur even in the absence of oestrogen. In the female rat, growth hormone combined with DCA, in the total absence of oestrogen, is capable of producing good duct growth.

The histological findings in human gynæcomastia show that the breast development consists almost entirely of duct proliferation. If one can apply the results of the above-mentioned experiments on rats to man, it seems as though oestrogens, although important, may not be an essential factor in the production of this type of development. It has been shown that pituitary dysfunction occurs in patients suffering from malnutrition and that normal pituitary function is restored during refeeding (as is evidenced by the increase in FSH in the urine). It becomes possible to postulate that the onset of gynæcomastia may be caused by an increase not only of oestrogen, but also of a variety of trophic hormones produced by the recovering pituitary gland.

Obesity. Widdowson⁷⁹ stated that fat women, on the whole, had large fat babies who grew big, reached an early puberty, and later became fat mothers. They had one advantage, that of producing more milk than thinner women. The claim that fat children tend to have an early puberty may not be generally accepted, but a number of studies, of which that of Wolff⁸¹ is recent, have indicated that this is indeed the case.

Certainly in adult life obesity appears quite frequently to be connected with amenorrhœa or menstrual irregularities^{52, 67} yet there is no evidence that the overall fertility is impaired in obese women as a whole.^{47, 80}

The Pancreas and Carbohydrate Metabolism

Overnutrition and undernutrition both produce disturbances in carbohydrate metabolism, but it is difficult to assess the role of the pancreas in these conditions.

Obesity. The close relation between obesity and diabetes is well known. Simple reduction of weight by dieting is sufficient to afford good "control" of the diabetes in a large proportion of obese dia-

betics, and in many of these even the glucose tolerance will then revert to normal. On the other hand, many obese, even grossly obese subjects, never develop diabetes, and retain normal glucose tolerance even when the extra stress of cortisone is added to their carbohydrate-regulating mechanism.²³ Beaudoin and his colleagues² believe that discrepant reports from different authors with regard to carbohydrate tolerance in obesity may partly be explained by the type or phase of obesity in the individual patients concerned. They examined two groups of obese women, one group being representative of "active" obesity (i.e. when gain in weight was actually progressing or the obesity was of recent onset), and the other group representative of "static obesity" (i.e. of long duration, normally since childhood, and not having increased for a long time). The "actively" obese subjects had a far higher tolerance to carbohydrate. These authorities remark further that previous writers have noted a tendency to hypoglycæmia during periods of rapid weight gain.

The actual mechanism of the production of diabetes by obesity is uncertain. The frequency of a history of diabetes in other members of the family and the comparatively small proportion of all obese subjects who have become overtly diabetic suggest that the obesity acts as an additional stress factor to an already damaged pancreas (or at least to an already insufficient carbohydrate-regulating mechanism). In other words, the patient concerned was previously "prediabetic", and the additional body mass was sufficient to overcome the ability of the pancreatic islet tissue to keep pace with the metabolic demands made upon it. Support for this idea comes from Mayer *et al.*⁴¹ and Mayer⁴² who showed that the pancreatic islets in his hereditarily obese-diabetic mice were hypertrophied, as though, teleologically, trying to keep up with the body's needs.

Other workers³⁸ believe that obesity produces an overstimulation of pancreatic cells followed by damage from overwork. There is no good evidence in favour of this hypothesis, and it does not accord with the clinical improvement in carbohydrate tolerance so often seen after relatively small weight loss. Others¹³ have suggested that the tendency to obesity and diabetes are inherited as connected genetic factors.

The converse situation, namely a diminution in the incidence of diabetes in countries subjected to forced dietary restriction, is well attested. One of the latest reports comes from Japan. Goto and co-authors²⁶ found a great drop in total numbers of diabetics, particularly of the mild type, in the late years of the Second World War and the years immediately following it. They agree that other factors

may have played some part, but believe that a reduced caloric intake was the most important.

It seems to be generally recognized that the incidence of diabetes among the more backward races is low, as long as they remain in their native habitat. On becoming urbanized, however, the incidence appears to rise. Recently this has been shown to occur among Zulus who came to live in the Durban area of South Africa.¹⁰ The exact place of altered dietary habits in their increased liability to diabetes is uncertain. The rural diet of the Zulu is very high in carbohydrate, and in general is quite adequate in calories. The possibility that an increase in fat intake may play some part in the liability to diabetes was also suggested by Schliak⁵⁸, who observed a sharp increase in diabetes in Germany in 1950, which was associated with a considerable augmentation of fat intake without a simultaneous increase in carbohydrate intake. On the other hand, the incidence of diabetes among the Eskimos, who have a very high fat intake indeed, is apparently very low.⁵⁹

Malnutrition. Chronic protein malnutrition, which manifests itself in young children as the syndrome of kwashiorkor, is responsible for gross changes in the exocrine function and histology of the pancreas. By contrast, the islets show little change, although increase in size of the islets, increase in the number of β cells and decrease in α cells have been reported.⁷ However, it is extremely difficult to test islet function, for a number of reasons which will be mentioned below.

Malnutrition and undernutrition have been shown temporarily to affect glucose tolerance.^{11, 12, 49} The great practical importance of disturbances in glucose tolerance is reflected in the opinion of some workers that sudden death in children suffering from kwashiorkor may be due to spontaneous hypoglycæmia.⁶⁹

Gillman and Gillman²⁴ report on oral glucose tolerance tests in 20 patients suffering from pellagra. They found a delay in the attainment of peak blood level (60–90 minutes). In 16 cases, the blood sugar remained elevated by 15–30 per cent above the fasting level after 3 hours. In 4 cases, there was a “flat” curve. Using intravenous glucose tolerance tests in 29 cases, they found that 22 had markedly delayed removal of glucose. Thirteen of 20 patients had abnormal glucose tolerance tests even after long periods of treatment and re-feeding in hospital.

A different approach to the problem is provided by the fact that some pellagrins are sensitive to small doses of insulin.²⁴ Perloff *et al.*⁴⁹ have shown the same in patients suffering from anorexia nervosa. Recent work on rats may suggest an explanation for this

oversensitivity, since it was found that insulinase activity in the liver was impaired by diets deficient in riboflavine, protein and pantothenic acid.¹⁴

The liver, the pituitary and adrenal hormones, and the pancreatic islets are all involved in the normal metabolism of glucose. It is difficult, therefore, to single out a deficiency of islet function as the cause of an abnormal tolerance test in cases suffering from chronic malnutrition, especially since the function of liver, pituitary and adrenal may all be abnormal in this disease. Although liver damage might be expected to play a major part in this glucose intolerance, a number of authors^{21, 31, 46} independently claim that there is no correlation between the pattern of glucose utilization and the histological appearance of this organ.

Recently it has been claimed that diabetes in the African is frequently caused by a variety of chronic pancreatitis with calcification.⁵⁷ This pancreatitis is considered to be different from the condition associated with gall bladder disease or chronic alcoholism, and to be related to chronic malnutrition.

Until such time as assays of the insulin content of the serum of malnourished subjects is performed and/or other more sensitive tests of pancreatic function can be found, it is not possible from the welter of conflicting information to infer how malnutrition affects pancreatic islet function.

The Thyroid Gland

Malnutrition has interesting effects on the thyroid gland. On the one hand, iodine lack induces gross enlargement and increased activity, while on the other, protein deficiency is responsible for atrophy and, possibly, reduced activity.

Goitre. It is now virtually certain that iodine lack in water and soil is the primary cause of endemic goitre.⁶²

Sporadic goitre (and in some cases even endemic goitre) is not due to lack of iodine, but either to a congenital enzyme deficiency or to the presence of substances which block the use of iodine by the thyroid gland. Goitre due to the latter cause is rare, but a proper understanding of the mechanisms concerned may provide a clue to the adequate pharmacological treatment of thyrotoxicosis. Such goitres occur sporadically in iodine-rich areas, in which cases removal of the specific goitrogen will prevent or alleviate the condition.

Fluorine. Fluorine as a cause of goitre has been reported from parts of England⁴⁵ and South Africa⁶³, and in these areas is found in

large quantities in water and soil. Its use in the prophylaxis of dental caries is commonplace, but it has been suggested that it may be a potential hazard in certain areas, where, because of poor supply of iodine, it might prove goitrogenic.

The manner in which fluorine produces its effects is as yet unknown. It may be due to the substitution of fluorine for iodine in the thyroid hormone, thus rendering it inactive.⁶⁴ Recent studies by Galletti and Joyet²² have cleared up a few points. They found that just over one-third of their thyrotoxic patients responded to treatment with fluorine both clinically and from the laboratory point of view. Others responded by showing decreased I^{131} uptake and protein-bound iodine (PBI) but showed no clinical improvement. I^{131} uptake studies indicated that fluorine acts by inhibiting the iodine-concentrating mechanism in the gland; but the most significant fact is that this did not occur in cases that had abundant iodine available in the blood. Contrary to other reports, radio-active fluorine studies did not show an accumulation of this element in the thyroid. It thus appears that fluorine will produce its goitrogenic effects only in areas where there is already a deficiency of iodine. Its use for short periods will not induce goitre. Conflicting evidence comes from areas in South Africa where it is thought that goitre is fluorine-induced in spite of the rich iodine content of the water.⁶⁴ The effectiveness of fluorine in inducing complete remission of thyrotoxicosis in some patients has been known for some time and the mechanism of its action may be worthy of further study.

Cabbage and Goitrogenic Foods. Cabbage has long been regarded as a goitrogenic vegetable. During the 1939-45 war, the increased incidence of goitre in certain areas was attributed to the use of cabbage as the main article of diet. Greer²⁸ reviews the very interesting history of the goitrogenically active Brassica family of plants of which cabbage is a member. Briefly, both the plant and the seeds of these vegetables contain a substance he calls goitrin, which is responsible for the development of the thyroid enlargement. It is thought that it may act by blocking the oxidation of iodide to iodine just as thiouracil is found to do. Goitrin exists in these vegetables in the form of a precursor "progoitrin", which is converted to the active substance by an enzyme that is destroyed in the process of cooking. It follows that unless the seed or plant is taken raw, or is left in water long enough for goitrin to form before cooking, it will not produce its goitrogenic effect. It has now been established, however, that cabbage itself contains relatively small amounts of goitrin and it is thought that its goitrogenic effect is probably due to its thio-

cyanate content. This view is further strengthened by the knowledge that added iodine is able to prevent cabbage goitre, but has no effect on goitre produced by the excessive intake of the substance contained in Brassica seed.

Greer²⁷ has reviewed fully the nutritional factors which may be responsible for goitre. The role played by calcium in the production of goitre is reviewed by Murray *et al.*⁴⁵ and Taylor.⁷¹

Chronic Malnutrition. Apart from some animal work³⁷ there is very little evidence to show that the thyroid gland is grossly affected in chronic protein malnutrition. Zubiran and Gomez-Mont,⁸² who examined a total of 131 glands of malnourished adults at autopsy, state that the changes they found differ little from those found in the aged. Since most of the glands were obtained from young adults, they infer that there was some histological evidence of depression of thyroid function. Because of other factors, it is impossible to ascribe any of the clinical features in chronic malnutrition specifically to thyroid hypofunction. Interpretation of a moderately low basal metabolic rate (BMR), reduced I¹³¹ uptake, or low serum protein-bound iodine (PBI), is very difficult. In our present state of knowledge, there does not appear to be enough evidence to incriminate protein malnutrition as a cause of hypothyroidism.

Anorexia nervosa, which is really a state of undernutrition with a psychological background, produces more evident depression of thyroid function as shown by histological changes, low BMR, decreased I¹³¹ clearance and low PBI according to some authorities,⁴⁹ but such findings are not constant.³ There appears to be great variability from case to case.

The Adrenal Glands

There is abundant clinical evidence to show that chronic malnutrition affects the adrenal glands.^{1, 24, 30, 53, 82} It has been suggested that manifestations of hypoadrenalism are: anorexia, bradycardia, hypotonia, nausea, diarrhoea, abdominal crises, sensitivity to cold, mental confusion, anæmia, disturbed carbohydrate metabolism and loss of libido. While it is true that all these symptoms are frequently found in severely malnourished subjects, most of them might equally be ascribed to deficiency in pituitary or thyroid function, or to liver dysfunction or simply to chronic ill-health.

On somewhat firmer ground is the pathological evidence of adrenal gland involvement in chronic malnutrition. This evidence is by no means uniform. There seems to be a fairly clear-cut distinction be-

tween the effects of starvation and those of malnutrition. In man⁷⁵ and animals⁴⁴ starvation has been shown to produce hypertrophy of the adrenal cortex. This hypertrophy occurs mainly in the zona fasciculata, with reduction of the zona glomerulosa. This pattern has great significance since the zona fasciculata is generally believed to elaborate the cortisone-like hormones. It is thought that these hormones, by virtue of their catabolic activity, mobilize endogenous "sources of food" during periods of starvation. In chronic malnutrition on the other hand adrenal atrophy has been adequately documented.^{24, 30, 65, 73, 75, 82} Uehlinger⁷⁵ specifically mentions the marked atrophy of the adrenals in cases of chronic malnutrition as distinct from hypertrophy in cases of simple starvation. It appears that the adrenal requires the stimulus of reduced calorie intake to become hypertrophic. The work of Mulinos and Pomerantz⁴⁴ on animals confirms this very point. They showed that the atrophic adrenals of rats suffering from "chronic inanition" will hypertrophy in response to complete starvation. It is surprising that in the previously atrophic adrenal glands of these animals there appears to be considerable reserve which the stress of starvation is able to call forth.

Most reported estimations of adrenal function in chronic malnutrition have been based on measurements of 17 ketosteroids (17 KS), which are not the best indicators of adrenal activity. Nevertheless it has been shown that in most cases 17 KS are reduced in amount.^{34, 36, 51, 56} In some cases adrenocorticotrophic hormone (ACTH) has been given to test adrenal gland reserve and a poor response has been noted, again by the estimation of 17 KS only.⁸² Tests of adrenal responsiveness, using the estimation of 17 KS and 17 hydroxycorticosteroids (17-OHCS) before and after ACTH, in patients suffering from pellagra, have been performed in our laboratory. It has been shown that although there is some response to ACTH, this is not as good during the acute phase of the illness as that obtained during the period of convalescence or in normal controls. Similar results have been obtained from tests performed on children suffering from kwashiorkor.

In acute starvation it has been found that there was a considerable drop in 17 KS but not in 17-OHCS in experimental animals.⁷⁰ As an explanation the author claims that the maintained levels of 17-OHCS indicate a response to the stressful situation and that normal blood levels of glucose are only possible as a result of the action of the glucocorticoid adrenal hormones. It is important to note that liver disease may accompany clinical malnutrition and that

some of the changes in urinary and blood steroid levels may well result, in part at least, from a disordered hepatic steroid metabolism. Steroid metabolism in health and disease has recently been reviewed.⁸

Vitamins. There is no good evidence to show that vitamin C is a necessary factor in steroidogenesis, in spite of the large amount normally present in the adrenal cortex, and its great depletion during stress or administration of ACTH. In fact, it has been shown that there is an elevated level of urinary 17 KS and ketogenic steroids (KGS) in very ill scorbutic patients. The low 17 KS and KGS, present in the urine of less ill patients during the height of the disease, rose considerably after stimulation with ACTH.⁵⁰

In thiamin deficiency it has been shown that there was adrenal hypertrophy and increased steroid output in animals, and that this was followed by eventual exhaustion of the gland. Pantothenic acid deficiency produces similar effects.⁴³

Oedema. The oedema of malnutrition remains an intriguing problem. It is obvious that no single factor can be held responsible for its development. Low serum proteins and anaemia are probably contributory features. The role played by the adrenal is of great interest and is germane to this discussion. It is well known that there is an alteration in metabolism of electrolytes and water in these cases, sodium, potassium and chloride being mainly affected. In kwashiorkor, for example, there is severe depletion of potassium with a striking retention of this element during therapy.²⁹ Elkington and Huth¹⁶ have recently suggested that the adrenal plays little part in the genesis of electrolyte disturbances in adults suffering from anorexia nervosa; the few aldosterone estimations done in these adults have been normal. However, estimations of urinary aldosterone in our laboratories indicate that there is an increase in this steroid during the oedematous phase of kwashiorkor followed by a fall to low levels during the stage of diuresis in some cases. The role of pituitary antidiuretic hormone in this type of oedema has not been elucidated.

The Pituitary Gland

Evidence of pathological changes in the pituitary gland in patients suffering from malnutrition is well documented. Zubiran and Gomez-Mont⁸², who examined the glands of 101 chronically malnourished subjects, found that almost half showed atrophy, alteration in stroma with some scarring, pyknosis, increased vacuolation, and basophilic invasion of the posterior pituitary, while cellular atrophy and calcification were less frequently seen. Gillman

and Gillman²⁴ report similar findings in chronic malnutrition and pellagra and they also record the presence of colloid cysts. However, they state that there is no characteristic picture which can be ascribed to the effects of malnutrition or pellagra. Atrophy of the pituitary has also been described in a patient suffering from chronic malnutrition due to steatorrhœa.¹⁷ Uehlinger,⁷⁴ however, examined the pituitary glands of starved people and found hypertrophic changes in 26 of 36 glands examined; 5 showed dense central eosinophilia, 17 had an increase in chief and stem cells which in places formed adenomas, and 4 showed both chief cell proliferation and dense eosinophilia. We know of few reports in which histological changes in the pituitary gland of patients suffering from anorexia nervosa are described.⁸⁰

Clinically there is occasionally some difficulty in differentiating anorexia nervosa from panhypopituitarism^{18, 19, 49} and the same may be said of patients suffering from chronic malnutrition and malnutrition resulting from steatorrhœa. Confirmation of these clinical resemblances is to be found in the low urinary levels of gonadotrophins, œstrogen, 17 ketosteroids, and of corticosteroids, poor response to ACTH, low B.M.R. and low protein-bound iodine values, some of which have been commonly and fairly consistently reported in both anorexia nervosa, and malnutrition.^{18, 49, 56, 82} In some cases of anorexia nervosa only urinary gonadotrophins and œstrogens have been found to be abnormally reduced, while thyroid and adrenal function have been normal.^{3, 20} By way of further proof that malnutrition is the cause of the abnormal biochemical findings mentioned above, it has been shown that refeeding will restore them to normal^{18, 48, 49, 82}

Leathem³⁷ has reviewed the results of his own animal studies and those from the literature and shows that there is abundant evidence that the pituitary gland is reduced in weight during both chronic malnutrition and acute starvation. Despite its reduction in size its gonadotrophin content has been claimed to be normal or even increased in amount, and it has been postulated that there is a failure in the "release mechanism" of the gland.⁷⁶ The explanation of these curious findings is not clear. Leathem's³⁷ own experiments show plainly that there is a fall in pituitary weight and gonadotrophin content during chronic malnutrition over a long period. It is possible that the conflicting results might be explained by variations in the experimental period and also variations in the type of nutritional deficiency to which the animals have been subjected. In the case of the response of the adrenals for instance, the type of nutri-

tional deficiency was shown to be of supreme importance. It is noteworthy that the patients in whom Uehlinger⁷⁴ found pituitary hypertrophy were apparently the same as those in whom adrenal hypertrophy was described, i.e. subjects suffering from semi-starvation in concentration camps. It would appear that this type of undernutrition may actually stimulate the pituitary-adrenal axis.

Conclusion

There appears to be little doubt that malnutrition considerably alters the function of some endocrine glands. It seems that the effects vary with the type of malnutrition and its chronicity. In anorexia nervosa there are cases which show no good evidence of endocrine disturbance in spite of grossly defective nutrition, while in others the degree of undernutrition and endocrine disturbance closely parallel each other.

The hypertrophy of the adrenals in starvation and the atrophy in chronic malnutrition illustrate how very different these types of disordered nutrition really are. In chronic malnutrition, there is a slow depletion of the body's nutritional reserve—a subliminal process which, unlike starvation, does not stimulate a response of the pituitary-adrenal axis. Of great importance is the apparent reserve shown to occur in the atrophic adrenals of chronically malnourished rats by Mulinos and Pomerantz.⁴⁴ Just how far the atrophic process can go before no response to stress can be elicited, is unknown. This information is of practical importance in view of the reported death of a pellagrinous patient in Addisonian crisis,⁵³ and the frequency of sudden death in gross chronic malnutrition especially kwashiorkor. Suggestions as to the cause of this have included heart failure, hypoglycaemia, hypokalaemia and septicæmia. The failure of the adrenal to respond to additional stress such as that of acute infection, for example, should not be overlooked. This suggests that a controlled trial of supplementary adrenocortical steroids in the treatment of severely ill patients suffering from chronic deficiency diseases, such as pellagra and kwashiorkor, might yield some useful information.

It has also been shown that some glands are more sensitive to nutritional changes than others. Abnormalities of sexual function in both male and female patients tend to occur early. Paullada⁴⁸ claims to have shown that pituitary and ovarian function are the first to recover during the process of refeeding. Observations on prisoners of war by Klatskin *et al.*³⁵ have also shown that gonadal function returns early. From what has been said and from our own experience,

there appears to be little danger of permanent endocrine damage once the nutritional disorder is corrected.

Zubiran⁸³ has attempted to correlate the endocrine disturbances in malnutrition and has postulated a somewhat complicated hypothesis. Briefly he claims that, because of malnutrition, the tissues are unable to utilize available circulating hormones. The levels of hormones in the blood, which remain unaltered, provide no incentive for the pituitary to produce its trophic hormones. As a result, both the pituitary and its target glands undergo "atrophy". During refeeding, because of the greater utilization of hormones by the tissues, the pituitary is stimulated to produce its trophic hormones and this results in a response by the target glands. The increased urinary excretion of gonadotrophins and oestrogens in patients under treatment consistent with this suggestion.

Of greater simplicity is the idea that since all the organs of the body suffer in the process of malnutrition there is no reason why the endocrine glands should remain unaffected. Deprivation of protein for hormone production and tissue building, and lack of vitamins must surely have some direct effect not only on the pituitary itself, but on the other glands as well. It appears that the function of the pituitary and its target glands is set at a lower tempo in harmony with the depressed metabolic activity of the body as a whole. Atrophy of the glands will increase with the progress of the disease itself. Brock⁶ states that "malnutrition, whatever its cause or nature, leads first to disturbance of function and later to disturbance of structure". The endocrine glands appear to offer no exception to this generalization.

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CHAPTER 28

PROTEIN VALUES OF HUMAN FOOD

by

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INTRODUCTION

THE singular and plural of the term "protein" are often used indiscriminately. Breese Jones (1939) has pointed out that "The term 'protein', used as a class name to differentiate it from other substances, does not signify an individual compound. In fact, there are innumerable proteins differing from one another chemically and physically. They may have identically the same percentages of carbon, hydrogen, oxygen, nitrogen, and sulphur and still have very different properties." Proteins have, however, one feature in common; they all contain nitrogen—from 15 to 18 per cent. Much of the work done on total protein metabolism is indeed largely a study of the metabolism of nitrogen.

The special place of proteins in the diet was recognized by the Dutch chemist, Gerrit Jan Mulder, when he gave the name to this group of nutrients in 1839. The word is derived from the Greek "proteios" meaning "primary" or "first". Mulder wrote: "Without it (protein) no life appears possible on our planet. Through its means the chief phenomena of life are produced." Nearly half the dry matter of adult man is protein and next to water it is the most abundant material in the human body. About one-third of the protein is in muscle, one-fifth in bone and cartilage, one-tenth in the skin and the rest in the other tissues and body fluids, except bile and urine which do not normally contain protein. Proteins have numerous special functions in the body and for these special purposes no other substances can replace them. About one-third of the score or more amino acids of which proteins are composed are, like the vitamins and some fatty acids, "essential" to the body, i.e. they cannot be synthesized in the body and must therefore be supplied in the food.

Foods are sometimes classified into groups in terms of the functions of the nutrients which predominate in them, i.e. as "energy-yielding", "body-building" and "protective" foods. Proteins are pre-eminently body-building materials; in fact, their constituent amino acids are

sometimes called the "building stones of the body". They can also serve as a source of energy. And it can be argued that they have also certain "protective" functions. Because of their many roles, which are essential to life, the establishment of a satisfactory method of measuring the nutritive value of proteins in foods is of the utmost importance.

There are numerous metabolic inter-relationships between proteins, their constituent amino acids and other nutrients in foods. One important association is between some proteins and the prosthetic groups of enzyme systems which are often one of the vitamins, notably one of those of the B-complex. For example, riboflavin is a component of several enzymes—the yellow enzymes—and the requirement for this nutrient in food may be influenced in some circumstances by protein in the diet and in others by the energy content of the food (Bro-Rasmussen, 1958). As knowledge grows, it will probably become increasingly apparent that there are few, if any, exceptions to the generalization that the function of single nutrients cannot be considered in isolation. This is particularly true of proteins. For example, the metabolism and therefore the nutritive value of protein are closely dependent on the protein : calorie ratio and the adequacy of the total calorie intake (Platt and Miller, 1958; Allison, 1958).

Ideally, the expression in chemical terms of data on nutrient requirements and on the amounts of nutrients present in foods is desirable. Efforts are being made to achieve this end with respect to protein, using the growing amount of information on essential amino acids in foods. Much more work is, however, necessary before this is fully practicable for human subjects and for human foods and diets. Meanwhile an attempt has been made to express "protein value" as a single figure, which is the main contribution described in this chapter. Requirements can also be expressed in the same terms.

This method of expression depends largely on the result of biological assays on young growing rats. As pointed out in the introduction to this volume, the emphasis in the papers presented is on human nutrition, although reference is also made to "nutrition experiments on animals when they are apparently relevant to the problems of man". The subject of species and age differences has recently been carefully examined by H. H. Mitchell (1959), who concludes that the requirements for growth for the rat, chick and pig, as well as the biological values for growing rats and mature human beings of egg albumin, whole egg, beef muscle, wheat gluten, casein and peanut flour, are similar.

The Committee on Amino Acids of the National Research Council U.S.A. (1959) reached a similar conclusion:

“Estimates of the quantitative requirements for the indispensable amino acids are available for several animals, adult men and women, and infants. Although different criteria have been used in both the experimental design and the evaluation of the data, two striking findings result: (a) the proportions of amino acids required are similar in all species, and (b) the requirements for the indispensable amino acids are surprisingly low. This uniformity in the pattern of amino acids required is interpreted to be a reflection of the similarities in the amino acid composition of the tissues of the different species.”

Although this presentation is concerned primarily with protein values determined experimentally by a method based on the retention of nitrogen, it should be recognized that in the feeding of human infants and of young animals the physical properties of the food supplying the proteins, i.e. milk, may be of paramount importance; thus, the structure of the clot formed in the infant stomach and the behaviour of the curd and whey fractions of the milk ingested may determine the nature and course of digestion of the milk proteins (Platt, 1960), and presumably affect the nutritional value of the milk to the consumer.

Of particular importance in relation to human diets are also palatability and acceptability, which are frequently associated with the protein-containing components of the diet. The protein-rich foods often determine what may conveniently be called “menu-value”, and protein values may be enhanced, or even sometimes adversely affected, by treatments, including cooking, used in preparing foods for consumption.

One outstanding problem remains to be solved, i.e. the protein requirements for optimal human health. In a recent report (NRC, 1959) it is stated that “the results of many investigators show considerable uniformity in the data on minimal requirements which are used as the baseline for estimating practical protein requirements”. The Report, however, adds that “further research and methodology . . . are needed to answer the controversial question of what constitutes an optimal intake” of protein. A primary difficulty is the assessment of “state of health” (see Taylor and Keys, 1958); this will be obvious from the definition of “health” in the Charter of the World Health Organization, as “a state of complete physical, mental and social well-being”. Difficulties arise even when the

problem is comparatively simple, as, for example, in determining the relative merits for human infants of breast milk and substitutes based on cow's milk. Mellander *et al.* (1959) maintain that criteria for optimum growth, development and performance at maturity have not yet been established and they agree (p. 29) that the comments on this question by Platt and Moncrieff (1947) are still valid.

HISTORICAL

Some of the earliest work on the chemistry and physiology of proteins is associated with the names of Magendie, Mulder, Liebig and Boussingault (Beach, 1948) who worked and wrote in the first half of the nineteenth century. It is 100 years since Karl Voit, called by Cathcart (1921) "the master and founder of modern metabolic research", published his first work (Voit, 1857). Voit was the first to set up a standard of protein requirements; he recommended for moderately active men 118 g. protein a day. He also demonstrated experimentally the importance of fats and carbohydrates as well as of protein in the diet. Fifty years ago Karl Thomas (1954) began making experiments on himself which led to a quantitative determination of the biological values of proteins; the essentials of his method are still valid.

Towards the end of his life, Cathcart (1940) delivered the Oliver-Sharpey lectures before the Royal College of Physicians of London on "The Mystery of Alimentation". In these lectures he reminded his audience of what he called "the shaky foundations of nutritional knowledge". Out of his intimate knowledge of protein physiology, Cathcart raised a number of points of profound interest, one of which will be referred to again—"the assumption . . . that the biological value of a protein is something static". In the same year that these lectures were delivered, a comprehensive statement was published by one of Cathcart's students (Cuthbertson, 1940-41). Cuthbertson examined several aspects of the subject which have not been considered here and his review is valuable as an indication of the state of knowledge at the beginning of what may be regarded as a new phase of progress in knowledge of protein nutrition.

Although the study of proteins has been continuous for over a century and much progress has been made, it was somewhat eclipsed between the two World Wars by research on vitamins. Already in retrospect (Platt 1954-55) it is becoming clear that just as vitamin research derived an impetus from the first World War, so protein research has been stimulated by developments during and since the second World War; three prominent ones are:

(i) The attention devoted by national and international agencies to the nature and prevalence of some forms of protein malnutrition: contributing to this development are the observations on, and sometimes the personal experiences of, prisoners of war; investigations of the effects of post-war food shortages on human health, and the urgency of the need for increasing food supplies to meet the nutritional needs of the world population, which is expanding at an unprecedentedly high rate.

(ii) The recognition of the life-saving value of blood and plasma transfusions—in the treatment of war wounds, injuries, burns and in surgical procedures, as one of the triumphs of present-day therapeutics; it is not always remembered that proteins constitute over 90 per cent of the total solids of whole blood, about 80 per cent of those of plasma and that a litre of blood contains about 200 g. of protein.

(iii) Atomic research and developments which have provided a variety of isotopes, the use of which has increased the range and volume of investigations into protein metabolism.

A catalogue of the factors that have contributed to progress in the study of proteins would also include:

(1) The isolation, characterization and studies of the structure of the proteins by physicochemical means, e.g. by electrophoresis,* by different types of spectrometry and by electron microscopy.

(2) Discovery of new methods of identification and estimation—especially by chromatographic techniques, of the amino acid components of proteins.

(3) The advancement of the study of the role of proteins in immunity against disease.

(4) The growth of knowledge of the nature and properties of enzymes, genes and viruses.

(5) The collateral development of knowledge of the chemistry of micro-organisms—especially of the effects of antimetabolites, antibiotics, and other chemotherapeutic agents.

(6) Discoveries—which are probably only the forerunners of many more—of the relationship between the anabolism and catabolism of protein and the activity of several endocrine glands (Platt, 1954–55).

A brief statement by Burgess and Aykroyd of the recent increased interest in proteins in nutrition is to be found in the foreword to the report of the proceedings of a conference held in Princeton in 1955 on “Human Protein Requirements and their Fulfilment in Practice” (Waterlow and Stephen, 1957). Two additional items deserve special mention in the history of the development of interest in proteins; one

is the survey by Brock and Autret (1952) of kwashiorkor in Africa; the other is the Second Inter-African (CCTA) Conference on Nutrition (CCTA, 1952) devoted to the subject: "Malnutrition in African mothers, infants and young children". This Conference immediately preceded the Third Session of the Joint FAO/WHO Expert Committee held in the Gambia in 1952 and was concerned exclusively with protein malnutrition.

In the Princeton report it is stated that "Terroine emphasized the distinction between the *physiological requirement*—the minimum amount of protein that will maintain nitrogen balance—and the *hygienic requirement*—the amount needed under the stresses of everyday life. The former can be defined with precision, as was done by Rose. The latter is at present a matter of guess-work." Experiments are described in the report, the results of which may also "provide a rational basis for the concept of a 'margin of safety', and so make it possible in the future to define with more precision Terroine's 'hygienic requirement'" (Waterlow and Stephen, 1957, p. 69).

Report of the FAO Committee on Protein Requirements

This report (FAO, 1957b) is a provisional one and its quantitative recommendations are tentative. The Committee recognized the tendency to give unjustifiable precision to data on dietary requirements for proteins and "tried to counteract this tendency by using careful and guarded phraseology, by hedging its recommendations with the necessary qualifications, and by insisting on the need for further research". Great credit is due to the Committee for its courage, and not least for what is perhaps the main contribution of the report as a whole, i.e. that it indicates "the direction in which the problem of protein requirements is moving". Two main developments in the report are (1) the expression of human requirements in terms of a "reference protein" of high nutritive value; and (2) the adoption of a provisional pattern of essential amino acids for man, which provides a basis for estimating the nutritive value of a diet from its amino acid composition.* The Committee was fully aware of the difficulties and uncertainties of the subject and therefore of the need for skill, caution and more knowledge in defining protein require-

* From data on the essential amino acid composition of three groups of six different proteins, Fisher (1954) has derived figures for the amino acid composition of "ideal protein". It is noteworthy that for six of seven essential amino acids, the pattern of "ideal protein" more nearly resembles that of the "provisional amino acid pattern" (FAO, 1957b) than does that of the protein of whole egg, cow's or human milk.

ments. Nevertheless progress has been made in solving the practical problem of planning food production and distribution in relation to the protein needs of populations. The FAO report will, for some time to come, constitute a challenge to its critics to engage in constructive research on the practical and scientific problem of protein requirements.

SPECIAL PROBLEMS IN EVALUATING THE PROTEIN ELEMENT IN HUMAN NUTRITION

Many of the difficulties of prescribing a diet for the human subject are inherent in the subject rather than in the food; the factors relating to the consumer will, however, be considered in a later section. So far as foods are concerned, it should eventually be possible to characterize the nitrogenous elements in them so that their "protein value" may be largely, if not entirely, determined by chemical or biochemical means. The problem is probably an easier one to solve for animal than for human nutrition. In animal feeding, standardized rations are usually given to animals which have a restricted and reproducible range of physiological functions, with the aim of achieving a limited prescribed result for commercial purposes. With human beings a number of difficulties arise, including (a) the complexity of the diets eaten by man, (b) the nature and timing of snacks and meals, and (c) the effect on food values of cooking and food processing.

Methods of Testing

Since the work of Magendie it has been known that the quality of proteins can differ widely and much effort has been devoted during the last 100 years to methods of evaluating these differences. Broadly speaking, there are three types of test, based on the measurement of different criteria:

- (i) Body weight, e.g. Osborne and Mendel (1917).
- (ii) Changes in specific organs or tissues, e.g. Whipple (1948).
- (iii) Nitrogen balance, e.g. Mitchell (1923-24).

The first two are generally simpler to carry out than the last, but tend to be less reliable. While determination of the nitrogen balance has until recently been tedious and slow, it has constantly been used as a method of assessment. In the method proposed by Thomas (1909) and developed by Mitchell (1923-24), the two parameters determined are (a) Digestibility, defined as the percentage of intake nitrogen which is absorbed; and (b) Biological Value, the percentage of absorbed nitrogen which is retained (see Table 1). Careful dis-

tion is necessary between these definitions and other common connotations.

TABLE I
Some Terms and Definitions

<i>Term</i>		<i>True</i>	<i>Apparent</i>
Digestibility (D)	$\frac{\text{Absorbed}}{\text{Intake}}$	$\frac{I - (F - F_k)}{I}$	$\frac{I - F}{I}$
Biological Value (BV)	$\frac{\text{Retained}}{\text{Absorbed}}$	$\frac{I - (F - F_k) - (U - U_k)}{I - (F - F_k)}$	$\frac{I - F - U}{I - F}$
Net Protein Utilization (NPU = D × BV)	$\frac{\text{Retained}}{\text{Intake}}$	$\frac{I - (F - F_k) - (U - U_k)}{I}$	$\frac{I - F - U}{I}$
		$\frac{B - (B_k - I_k)}{I}$	$\frac{B - B_0}{I}$

	<i>Nitrogen Free Diet</i>	<i>Test Diet</i>
Intake nitrogen	I_k	I
Faecal "	F_k	F
Urine "	U_k	U
Body "	B_k	B
Initial body		B_0

More recently a rapid method for the determination of the product of Biological Value and Digestibility has been developed (Miller and Bender, 1955); this measurement is termed Net Protein Utilization (NPU), and is the percentage of nitrogen intake that is retained. In this method nitrogen balance is estimated directly by analysis of the carcass rather than of the urine and faeces. Assays are made under standardized conditions with respect to the level of protein fed and amounts of fat, minerals and vitamins in the diet. The term Net Protein Utilization (standardized), or NPU (st.) for short, has been applied to the results of these assays (Platt and Miller, 1959).

Efficiency measurements of this sort cannot be directly applied to human diets because, as mentioned earlier, Net Protein Utilization is not static. The role of the energy value of the diet as a factor affecting protein utilization was emphasized as long ago as 1890 by Hirschfeld. Work on this subject, which has recently been reviewed (Munro, 1951; Allison, 1958) demonstrates that protein may be spared by the addition of either fat or carbohydrate or both.

Conversely, the value for NPU falls when the protein to calorie ratio is raised above a certain level, an effect shown by Hamilton (1939) and measured quantitatively by Miller and Payne (1960). For example, the biological value of casein may be halved by trebling the protein concentration in the diet. These findings may be disquieting to those accustomed to measure NPU by feeding protein to laboratory animals at a fixed level (usually 10 per cent). Surveys show that man may have less than 6 per cent total protein (Platt, unpublished) in his customary diet or as much as 60 per cent (Cuthbertson, 1940-41).

Not only is the protein : calorie ratio important, but also the total energy intake per day. If this is reduced below a certain level, protein is burned for energy purposes, and efficiency of utilization therefore falls (Allison, 1958): thus Forbes and Yohe (1955) show no change in the biological value of a diet when the food intake of rats was reduced from 8 to 6 g. per day, but a fall from 99 to 69 when the food intake was further reduced to 4 g. per day. On the other hand, Allison (1958) shows that the utilization of whole egg was not reduced when fed to dogs in a diet containing only 50 per cent of the required calories. Work now in progress (Miller and Payne, 1960) indicates that composition of the diet must also be taken into account if this effect is to be fully understood, but there is little doubt as to its importance in practical diets (Fox, 1959; Dema, 1959, see table 2, p. 367).

The effects of vitamins and minerals are less spectacular, at least in short-term experiments; examples of these effects may be found in the work of Henry and Kon (1956) with vitamin B₁₂ and that of Menaker (1954) with magnesium salts.

NET DIETARY-PROTEIN VALUE

In the past it has been customary to use qualitative expressions which extend quantitative estimates of the protein content of foods. Thus, protein may be described as being of "animal" or "vegetable" origin, as "first" or "second" class, or as "high quality" or "low quality". Quality may also be expressed numerically in terms of "Biological Value" determined under prescribed conditions on single proteins, single foods, or on combinations of proteins and foods. Clearly there is a need, in practical nutrition work, for a method of expressing the protein value of foods in a single figure which takes account of both quantity and quality of the protein and of the effects on these of various factors in the diet as eaten. Such a method has been worked out (Platt and Miller, 1959).

Net dietary-protein values are determined by assays on rats, by feeding *ad libitum*, after freeze-drying, dishes, meals or diets ordinarily eaten by man. The technique for measuring NPU introduced by Miller and Bonder (1955) is used; but without making any adjustments in the level of protein and the amount of vitamins or minerals in the mixtures assayed. The results obtained are values for what is called Net Protein Utilization (operative)—NPU(op)—and are a measure of the quality of the protein. The quantity of protein in a mixture is expressed as the proportion of the metabolizable energy, i.e. physiological calories (see Miller and Payne, 1959) which could be derived from it: this is called protein calories per cent.* The product of quantity and quality is termed Net Dietary-protein Calories per cent (NDpCals per cent):

$$\text{NDpCals \%} = \text{NPU(op)} \times \text{protein Cals \%}$$

This term represents the utilizable protein in the mixture and is a function of both quality and quantity; it may be translated into French as Valeur Proteique Nette de la Ration (VPNR) and should be distinguished from a term proposed by Mitchell (1922) "Net Protein Value", which is obtained by multiplying NPU(st) by the crude protein content and is useful for comparing materials rich in protein.

In the method for determining Net Dietary-protein Values normal young growing rats are fed *ad libitum* and are kept in controlled environmental conditions. Such animals have a large nitrogen demand and the values obtained must be regarded as maximal. It therefore seems reasonable to regard these values as indicating the potential nutritive value of the diet. Full use of the protein value of diets will not be made by animals receiving an inadequate amount of calories, nor in animals showing certain physiological or pathological conditions which are considered on pp. 364–369.

The FAO Committee (1957b) expressed values and requirements in terms of a "reference protein" which theoretically should contain 16 per cent nitrogen and be completely utilized. The protein values of diets are calculated in terms of the "reference protein" by "scoring" their amino acid composition against a provisional pattern of amino acid requirements for man. Net Dietary-protein is clearly equivalent

* Protein Calories % = Nitrogen % \times 6.25 \times $\frac{4}{\text{Cals./g.}}$ = $\frac{25 \text{ N \%}}{\text{Cals./g.}}$

to "reference protein", but there are, in the present state of knowledge, advantages in the use of a biological method for determining protein quality.

METHODS FOR PREDICTING PROTEIN VALUES

Willcock and Hopkins (1906) established the concept that the nutritive value of proteins could be interpreted in terms of amino acid composition; more recently the emphasis has passed to content of essential amino acids (Block and Mitchell, 1946). This raises the possibility of determining protein value by chemical means. Some success has been achieved in predicting NPU(st) from protein scores based on amino-acid analysis (FAO, 1957b), but in ordinary human diets the NPU(op) is not directly related to the amino acid content (Drury and Miller, 1959). A method of correcting protein scores based on the latter, by allowing for the effect of protein concentration, has been put forward by Miller and Payne (1960).

These authors measured the NPU(op) of a number of diets containing the same protein at different levels and derived a general equation for this purpose. Their results may be conveniently expressed in the form of a nomograph (Fig. 1) which illustrates the relationship between NPU(st), NPU(op) and NDpCals per cent over a wide range of protein concentration in the diet. The following are some examples of how the nomograph may be used.

(1) *Calculation of NDpCals per cent.* This may be achieved, given an estimate of the protein quality, either directly as NPU(st) or obtained indirectly:

(a) from the "protein score" based on a knowledge of amino acid composition (FAO, 1957b); (b) from estimations by a quick short column chromatographic determination of S-amino acids and lysine, together with a separate colorimetric determination of tryptophan (Lewis, 1960); (c) from total S content for food mixtures (Miller and Naismith, 1958).

NDpCals per cent can be read off the nomograph at any concentration of protein in the diet.

(2) *Calculation of NPU(op).* NPU(op) depends on both "score" and protein concentration; it may be calculated simply by dividing the value for NDpCals per cent by that for protein Cals per cent.

For maintenance, rats are found to need a diet in which NDpCals per cent = 4. Below maintenance NPU is constant, i.e. NPU(op) = NPU(st). Above the maintenance level, NPU(op) falls with increase in protein concentration. The extent of this fall may be determined

from the nomograph by laying a ruler from that point on the hyperbola NDpCals per cent = 4 corresponding to the "score" in question, to the point marked X on the protein concentration axis (Fig. 1).

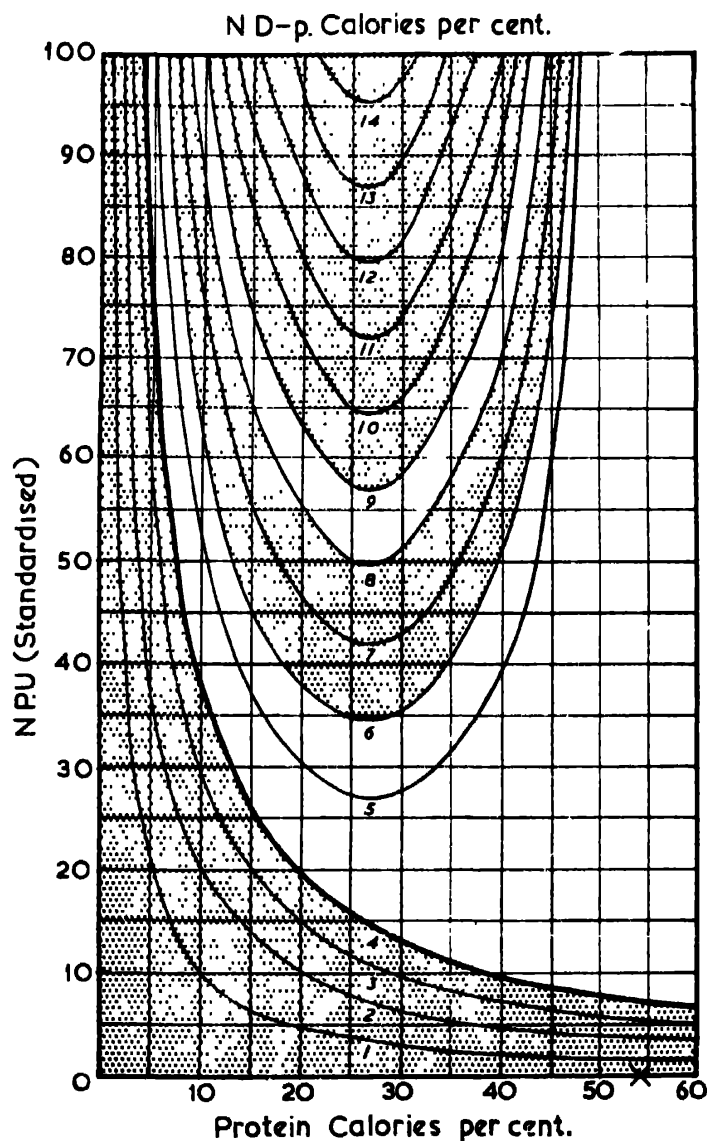


FIG. 1. Nomograph for the production of protein values. The numbers on the curves in the nomograph are units of protein value expressed as NDpCals per cent.

(3) *Calculation of Maximal and Minimal Protein Values.* The lowest possible protein score, or, alternatively, the lowest concentration of protein in a mixture required to achieve any given NDpCals per cent may be seen from the nomograph. For example, NDpCals per cent = 8 (i.e. the level required for young children)

cannot be reached by diets having less than 9 per cent protein, whatever the quality, nor with protein having a score, or NPU(st), of less than 50, whatever the concentration.

The maximum NDpCals per cent that can be obtained from any protein, whatever the score, is at 27 per cent protein calories. For example, the highest possible protein value of a diet based on a protein having a score of 35 would be 6 per cent NDpCals. The range of NDpCals per cent is 0–14·7 per cent.

(4) *Calculation of the Protein Value of Supplemental Diets.* When protein-rich foods are added to a diet, the protein value is in general influenced by two factors: the first, and usually more important, is the resultant increase in concentration of protein. Secondly, by accident or design, the amino acid pattern may be improved. However, since 75 per cent of foods, dishes and diets, and most of the protein supplements investigated by us, have been found to be limited by the same amino acids, namely those of the S-containing group, this effect is usually only of secondary importance.

Examples of both types of supplementation are illustrated below:

EXAMPLE 1. What is the “protein value” of a meal consisting of bacon, eggs and beans? The composition of the meal is:

	<i>Protein</i>	<i>Protein Cals.</i>
	<i>g.</i>	<i>per cent</i>
1 egg	7	30
2 oz. bacon	7	11
4 oz. baked beans	7	26
Total values	21	22

Knowledge of the amino acid contents of the components indicates that the protein value of the meal is limited by S-amino acids:

Egg, bacon and beans contain respectively 342, 170 and 126 mg.* of S-amino acid/g. N, with a mean of 212.

Therefore the protein score = 78 . . . (FAO, 1957b) = NPU(st). NPU(op) = 50 at 22 per cent protein Cals. . . (from nomograph Fig. 1) and NDpCals = 11·0 per cent from nomograph. The value for this food mixture determined by the rat assay method was NDpCals = 10·6.

EXAMPLE 2. What is the “protein value” of (a) wheat; (b) beans; (c) sesame; (d) a mixture of wheat (2 parts), beans (1 part), sesame (1 part).

* Values taken from Orr and Watt (1957).

The prediction is shown as follows:

	<i>Protein Cals*</i> <i>per cent.</i>	<i>"Protein score"†</i> <i>= NPU(st)</i>	<i>NPU(op)‡</i>	<i>NDpCals per cent.‡</i>
Wheat . .	11	47	45	5.0
Beans . .	31	47	24	7.4
Sesame . .	14	59	50	7.0
2 parts wheat 1 part beans 1 part sesame	15	70	55	8.2

The value for this mixture determined by assay on rats =
NDpCals 7.8

* Platt (1945); † FAO (1957b); ‡ from nomograph (Fig. 1).

NET DIETARY-PROTEIN CALORIES (NDpCals) AND THE CONSUMER

Attention has been drawn on p. 359 to the biological meaning of the term Net Dietary-protein Value as determined under the conditions described. It should be emphasized that the protein value or NDpV of a food mixture is the measure of its maximum potential value as a source of protein. There are, however, a number of factors which may affect the consumer in which full use will not be made of the protein value of the food eaten. Therefore, although the Net Dietary-protein Value of the diet does not alter, consideration must be given to the protein value to the consumer of the diet (*a*) in various physiological states, (*b*) when the supply of food eaten is restricted in amount, and (*c*) when the protein in the food is not wholly utilized for normal physiological purposes because of various pathological conditions.

Physiological States

Many attempts have been made to evaluate human protein requirements. Three of the more recent are represented in Fig. 2; all the values are expressed in terms of protein which is completely utilized. These curves all show relatively high requirements for the infant and very low requirements for the adult. It is reassuring in this connection that a NDpV of 8 has been obtained for human breast milk (Platt and Miller, unpublished). The values shown in the figure are based on the protein requirements for both maintenance and growth and do not take into account the so-called "hygienic

requirements" suggested by Terroine (Waterlow and Stephen, 1957). In this context, it may be noted that the FAO Committee (1957b) allowed extra protein during puberty, having in mind

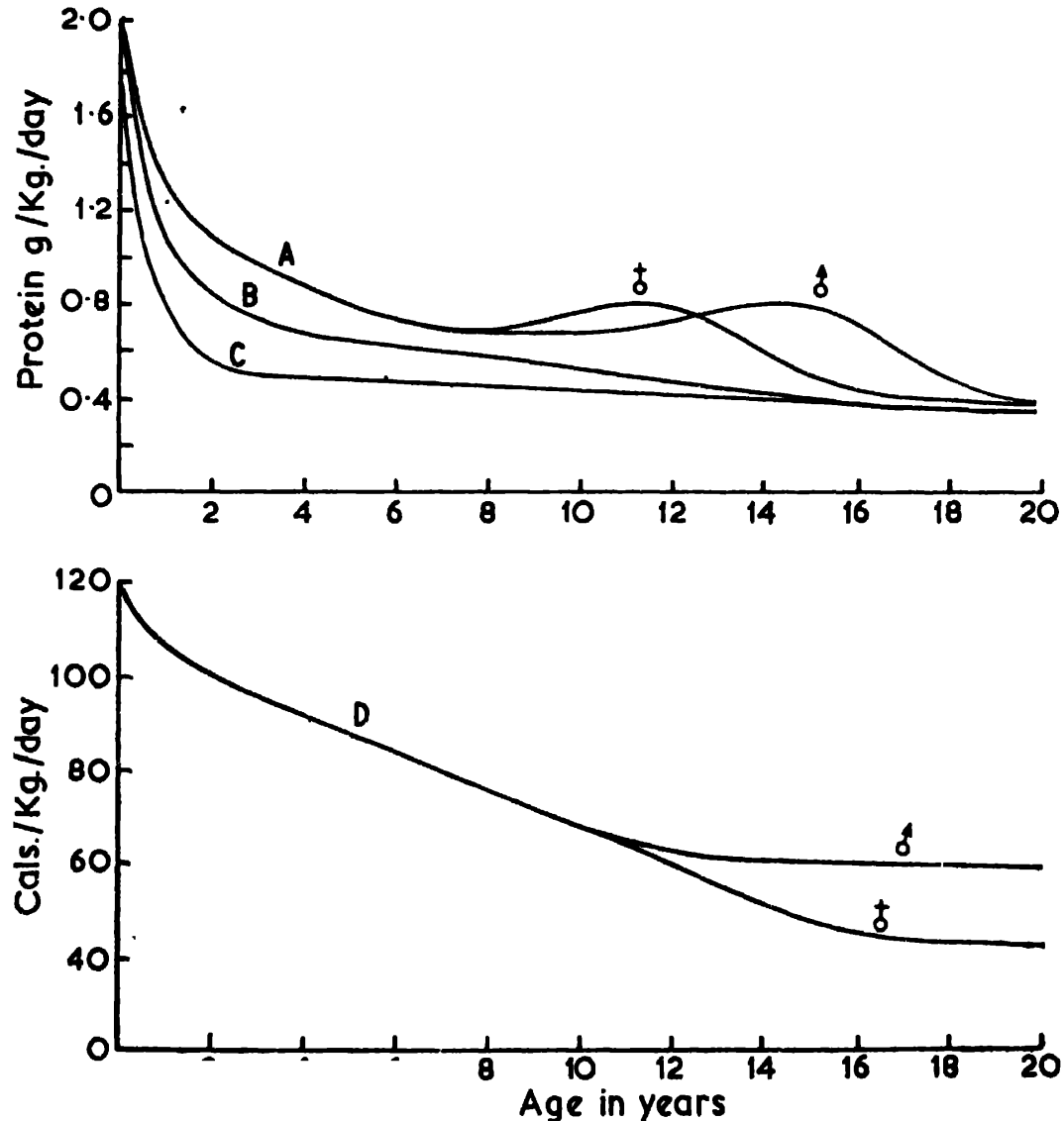


FIG. 2. Protein and calorie requirements for human subjects at various ages.

Curve A: from "average minimum requirements for protein". (SAO, 1957b).

Curve B: from "minimum protein requirements" (Hegsted, 1959).

Curve C: from "NRC" (1959).

Curve D: from "SAO" (1957a).

particularly the work on tuberculosis in the adolescent female (Johnston, 1953).

The calorie requirements for man (FAO 1957a) are given in Fig. 2, curve D. Using these data and the minimum requirements for protein

expressed in curves A, B and C (Fig. 2) and allowing "an arbitrary increment of 50 per cent over average minimum requirements" (FAO 1957b) to take care of individual variations, protein allowances as shown in Fig. 3, curves A', B' and C' are obtained. It will be seen (curve A'), that the allowances for puberty made by the FAO Committee on Protein Requirements appear to be large compared with those for infants and some adjustment may be needed. The protein allowances shown in Curve C' for the age group 1-4 years

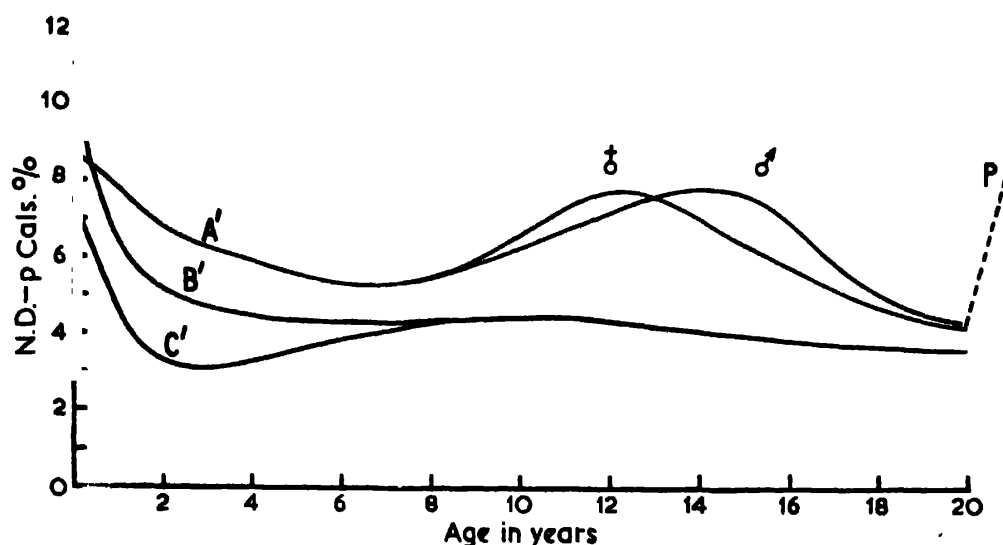


FIG. 3. Protein allowances for human subjects at various ages expressed as NDpCals per cent employing data set out in Fig. 2.

Curve A—from A and D.

Curve B—from B and D.

Curve C—from C and D.

P = Pregnancy.

L = Lactation.

Values include "safe practical allowances" calculated by the method of SAO (1957b).

are lower than those for the adult, a recommendation which would appear to require further consideration in view of the clinical evidence that this is the age group most prone to protein malnutrition. On the whole, the data shown in curve A' of Fig. 3 are probably the most acceptable.

Also presented in Fig. 3 are the requirements for pregnancy and lactation (P and L), based on the daily increments of protein recommended by the FAO Committee (1957b). It will be seen that the highest requirements for protein among all the groups are assigned to nursing women.

There is little evidence that the protein requirements are quantitatively different in old age or for human subjects engaged in heavy

work. Nevertheless, these physiological states occur at two extremes of the range of calorie intakes. Clearly, if stated in terms of grams per day the protein requirement is the same in both, expressed as NDpCals per cent it will be very different. Thus elderly people require a higher concentration of good quality protein in their diets than do manual workers.

Much of the knowledge of the nutritive value of food comes from chemical analyses and it must be pointed out here that, whilst these provide useful information, they do not, as pointed out by Gilbert and Gillman (1959), always allow "predictions to be made regarding the impact of any food or combination of foods on the intact organism. Such information could only be obtained through biological experimentation, preferably in animals at different stages of growth and development." There is also evidence, and further experiments are in progress (Ross, 1959), which suggests that the pattern of disease in later life can be altered by the nature of the diet eaten throughout life. Such observations reveal problems which will only be resolved after much more research.

Underfeeding

As mentioned on p. 359, the caloric intake has an important effect on the use which is made by the consumer of the protein of the diet.

Table 2 shows this effect for a number of human diets. When the energy intake is low in relation to requirements, some protein is used as a source of energy and is not then available for anabolism. Almost all the Jamaican diets would be adequate for young children if they were consumed in amounts sufficient to meet caloric requirements; nevertheless it is well known that protein malnutrition is common in young children in Jamaica.

TABLE 2

Showing the Impaired Utilization of Some Human Diets when fed in Restricted Amounts

DIET	NDpCals	$\frac{\text{Cals. (restricted)}}{\text{Cals. (unrestricted)}} \times 100$	$\frac{\text{NDpCals (restricted)}}{\text{NDpCals (unrestricted)}} \times 100$
	<i>per cent.</i>		
Jamaican 7	9.2	60	40
" A	9.1	71	46
" 5	8.0	70	42
" B	8.0	64	40
" 4	7.4	50	40
Nigerian 3A	7.4	84	47
Jamaican 3	6.8	77	62
Nigerian 3B	4.5	74	29

The effect of reducing the caloric intake is illustrated in detail in Fig. 4 for a Persian diet fed over a wide range of caloric intakes. By selecting the unit for calorie intake as $\text{cals./day/wt.}^{0.73}$ size and species differences should be eliminated and the figures obtained ought to be directly comparable with intakes for man, because basal energy expenditure has been shown to have a linear relation to

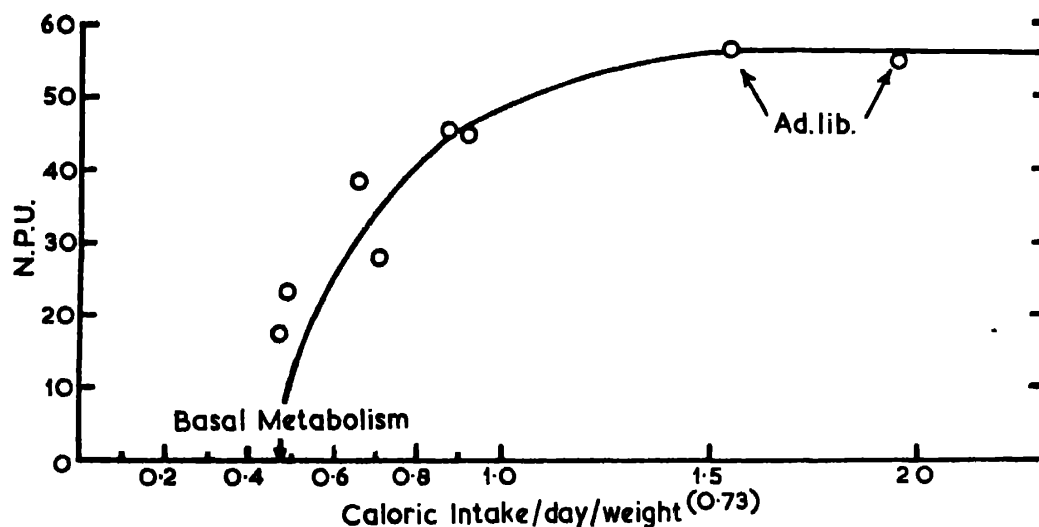


FIG. 4. The impaired utilization of a Persian diet when fed in restricted amounts.

body weight to the power of 0.73 for all species (Brody, 1945). In this context it is of interest to note that the curve drawn through the points obtained experimentally cuts the abscissa at a point corresponding to basal metabolism. Caloric intakes as low as $0.74 \text{ cals./day/wt.}^{0.73}$ have been reported amongst Persian children (Hedayat, 1960) and reference to Fig. 4 indicates that the NPU would be halved.

Food requirements may be increased and therefore underfeeding may also occur in patients with injuries, e.g. after burns or after surgical operations, since trauma may increase the basal metabolic rate; this may be one explanation of the need for increased attention which should be given to the nutrition of the hospital patient (see Bull, 1958). Loss of appetite during illness may also lead to underfeeding.

Pathological Conditions and Protein Needs

Some 12 years ago, in a study in a Gambian village, it was found that almost all the people examined showed signs of malnutrition thought to be due principally to inadequacy of protein in the diet, yet this could not be substantiated from the evaluation of the food

consumption data. It was, however, known that malaria was hyper-endemic in the area. This fact led to a consideration of the role of malaria and of infections and infestations generally in the pathogenesis of human malnutrition (Platt, 1957, 1958). Recent studies in this Unit have shown that in malarial infection in rats more profound changes in protein malnutrition occur in infected animals than in pair-fed controls (Dema, Miller and Platt, 1959) and that the former show a low efficiency in the utilization of food.

The following table shows the effects of infection on the protein value obtained experimentally of the diets for two communities in Nigeria (Kanuri and Otukwang; see Nicol, 1956). It will be seen that the value found for both diets is reduced to about one-half of that for the normal animal fed *ad libitum*. Approximately half of the reduction in utilization is the consequence of the poorer appetite of the malarious animals:

TABLE 3

Showing the Impaired Utilization of two Nigerian Diets when fed to Malarious and Pair-fed Rats

Treatment	NDpCals per cent.	
	Kanuri	Otukwang
Unrestricted, Uninfected	8.0	4.2
Malarious	4.3	2.2
Uninfected, Pair-fed	6.0	3.4

Undoubtedly the protein of ordinary diets will be less well utilized than it is by the normal individual in the numerous pathological conditions in which nitrogen is lost from the body in abnormal amounts or when, as for example in patients with new growths, protein is probably incorporated into new tissue at several times the normal rate (Frantz and Zamecnik, 1950). Several recent reviews are available on the effects of injuries and infections on nitrogen metabolism. (See, for example, Bull, 1958; Dohan, 1958 and Levenson and Watkin, 1959.)

Now that both the increased needs of the sick and the protein value of the food can be measured it should be possible to prescribe diets of appropriate protein value if and when necessary.

In their comments on protein requirements in pathological states, the FAO Committee (1957b) say:

"It would obviously be impossible for the Committee to make quantitative recommendations for requirements in varying acute and chronic pathological states. The Committee urges, however, that physicians and administrators should bear in mind the effects which such states may have on requirements."

The developments described in this chapter may renew the physician's interest in the feeding of patients, who may, like the healthy individual at rest in bed, lose nitrogen at the rate of 12–18 g. per day (Keys, 1944).

Further knowledge is needed of the characterization and significance of the level of protein nutrition. This level cannot be characterized merely by establishing that the subject is in nitrogen equilibrium, which may be achieved on a low-protein intake in an undernourished subject and at the physiological minimum with a higher intake in the normal individual. There is also the question of what constitutes the upper level of protein nutrition; is it a state of eutrophy (a term used by both Cathcart (1940) and Cuthbertson (1940–41) and attributed by the former to Virchow)—and if so, what is the nature and purpose of the protein stores or reserves? (For discussion of protein stores, see Waterlow and Stephen, 1957, p. 119).

SOME PRACTICAL CONSIDERATIONS

“Volumes have been written about the nutritive value of amino acid composition of isolated proteins or the proteins of separate foods, but for practical purposes much of this work seems to be in a nutritional vacuum. The proof of the pudding is in the eating and what is wanted is reliable assessment of the diets as eaten by animals or man, in health or disease, in plenty or want” (Henry and Kon, 1958).

This chapter has been mainly concerned with the development and application of a quantitative measure of protein value of diets which has been called Net Dietary-protein Value, and is most appropriately expressed in terms of Net Dietary-protein Cals. per cent. It takes account of protein quantity and quality and other dietary factors affecting the utilization of nitrogen by the consumer. In the Introduction the reader was reminded that the “menu value” of a meal is an important consideration in relation to the protein value of food and that, especially in infancy, the source of protein, i.e. breast milk, has special properties relating to the proteins it contains. One aspect of menu value for the young child is the form in which the food has to be given in order to supply the protein needs.

From the data in Table 4 it is obvious that the volume of the infant stomach and the limit imposed on food intake must be a factor of importance, indicating the need to provide protein-rich foods to subjects in this age group.

TABLE 4

Amount and Energy Content of Various Preparations needed to meet Protein Needs of a 2-year-old Child

("Safe practical allowance" (FAO, 1957b) 15.8×1.5 g. reference protein; calorie requirement (FAO, 1957a) 1203 cal.)

<i>Preparation</i>	<i>NPU*</i>	<i>Amount</i>	<i>Energy content (Cal.)</i>
Gruel: 20% sorghum meal in water .	50	2.3 l.	1,616
20% maize meal in water .	40	3.1 l.	2,219
20% cassava meal in water .	50†	15.7 l.	10,673
Bread (85% extraction) .	40	591 g.	1,327
Milk: cow's .	100‡	0.7 l.	427
human .	100‡	1.7 l.	1,194

* Approximate values.

† Guestimate: protein score 22 only.

‡ Assumed equal to "reference protein" with score = 100 (see FAO, 1957b).

For convenience some protein allowances in terms of NDpCals taken from curve A' of Fig. 3 are set out below:

TABLE 5

Calorie and Protein Allowances for different Age Groups

<i>Subject</i>	<i>Age Yrs.</i>	<i>Calories per day</i>	<i>Reference Protein g./day</i>	<i>NDpCals per cent.</i>
Infant .	0-1	—	—	8.0
Toddler .	1-2	1,230	24	7.8
Child .	4-9	1,970	29	5.9
Adolescent .	—	3,050	61	8.0
Adult .	—	2,960	34	4.6
Lactating mother .	—	3,200	76	9.5

As is well known, some age and sex groups, in particular the pregnant and lactating woman, need relatively more protein than, say, the male adult; this fact draws attention to one of the most outstanding practical problems in applied nutrition, to ensure that what have been called the "vulnerable" groups, receive a share of the family diet appropriate to their physiological needs.

The relationship between the protein values of average dietaries and of single meals and dishes is of interest. Since the supplementary action of protein is probably effective only if the proteins are consumed together, values for individual meals or dishes may be in some respects more pertinent than values for whole dietaries which will include food items consumed at intervals of hours or even weeks. It will, however, be seen from Table 6 that the values for

meals and diets in a region are similar to those obtained for the average diet for that region. These may be compared with the requirements given in Fig. 3. It should be noted that information is rarely available about the distribution of food within the family since the data obtained from food consumption surveys are often inaccurate.

TABLE 6

Mean NDpCals per cent of Meals and Diets from various Continents

	<i>Meals</i>	<i>Diets</i>
Europe . . .	10.6 (26)	8.8 (19)
Africa . . .	6.5 (23)	5.7 (17)
Asia . . .	6.0 (10)	6.7 (3)

The figures in parentheses indicate the number of samples assayed.

Wheat contains about 6 per cent NDpCals and a child on a diet based on wheat as the staple is likely to obtain his protein requirements. In fact, it would be difficult to devise a diet consisting mainly of wheat that did not have a NDpCals of 8 per cent. In sharp contrast, the dietaries of tropical peoples consuming starchy roots, tubers or fruits (e.g. cassava, sweet potatoes, yams, plantains or bread-fruit) as staple foods have a low, often a very low, proportion of protein calories and therefore of Net Dietary-protein Calories.

The assessment of "protein values" of foods—as meals or dietaries—in relation to the consumers' needs is of importance not only for the individual or the family but also on a national and world scale. In the second World Food Survey (FAO, 1952), supplies of protein in relation to "targets" for production were discussed in terms of grams of animal or vegetable protein per caput daily. It should now be feasible to examine data of this sort in terms of "protein values" as described in this chapter, thus assisting in the planning of production and distribution within and between communities.

Inevitably emphasis in this chapter has been placed on proteins in nutrition; in concluding, as in introducing the subject, the inter-relationship of proteins and other dietary essentials must be stressed for it cannot be reiterated too often that, "notwithstanding the importance of proteins in nutrition, for the growth, maintenance and rehabilitation of tissues, other nutrients must be supplied in the diet and a balanced diet of good food must remain the sheet anchor of treatment—curative and preventive" (Platt, 1954-55).

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CHAPTER 29

NUTRITION AND INFECTION

by

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THE increased attention now being given to the nutritional problems of tropical and other technically underdeveloped areas has resulted in renewed interest in the interrelationships between nutrition and infection. To a very large extent, the excessively high mortality in these areas is due to the combined effects of malnutrition and infection on an individual, a synergistic action which makes somewhat academic the question as to whether the infection or the malnutrition is the immediate cause of death. Not only mortality but also morbidity is increased because of this interaction. The resulting adverse social and economic consequences are a great handicap to the efforts and progress of developing countries.

This interaction is reciprocal in nature. As confirmed by both epidemiological and metabolic studies, most infections make the nutritional status worse if the individual is already consuming a deficient diet. On the other hand, if the individual is sufficiently well nourished, infectious disease is likely to be less severe and possibly less frequent. The data from epidemiological studies in human populations and from very extensive experimental work in animals clearly establish the practical importance of this type of synergism. Under certain experimental circumstances, which are thus far of no clinical or public health significance, specific nutrient deficiencies may also be antagonistic to the multiplication of certain pathogenic agents within the host.

Some of the evidence for these different types of interactions between nutrition and infection are reviewed in the following sections and some of the possible mechanisms discussed.

Malnutrition and Bacterial Infections. A recent review¹ cites over 100 articles published since 1928 which have dealt with the effect of nutritional deficiencies in various experimental animals including the pigeon, chicken, mouse, rat, guinea pig, hamster, rabbit, pig, monkey, and dog, and with only a very few exceptions, deficiencies of protein, B-complex vitamins, ascorbic acid and vitamin A made the infection

more severe. Neither mild starvation nor vitamin D deficiency appeared to influence resistance. Organisms used included *D. pneumoniae*, *M. tuberculosis*, Salmonella, Shigella, Corynebacterium, *P. pseudotuberculosis* and spontaneous mixed infections, and even the influence of nutrition on the effects of diphtheria toxin and tetanus toxin were studied.

Because of the greater severity of tuberculosis in malnourished populations²⁻⁷ noted under wartime conditions in Europe, the higher tuberculosis rates in Russian as compared with British and French prisoners of war^{8, 9} and in Danish internees not receiving Red Cross parcels,¹⁰ greatest attention has been focused on the role of nutrition in this disease. Leitch¹¹ has called attention to the Trondheim Naval Training School in which over a period of many years one-third of the cadets developed tuberculosis, a rate which was not lowered by better housing, but which promptly dropped to less than that for the country as a whole when fresh milk, meat and fruit were added to the diet. Downes¹² divided 194 negro families exposed to reinfection with tuberculosis into two groups matched for family size and supplied one group with vitamins and minerals for 5 years. The rate per 100 person years was 0.91 in the control group and 0.16 in the group receiving regular vitamin and mineral therapy. Since the numbers were small this difference was barely significant at the 5 per cent level. Getz *et al.*¹³ report serum levels of vitamins A and C to be lower in 28 persons subsequently developing tuberculosis than in over 1,000 individuals who did not develop this disease. It is also noteworthy that metabolic studies in both India¹⁴ and the U.S.¹⁵ have shown that a good prognosis is associated with strongly positive nitrogen balance.

Blackfan and Wolbach¹⁶ and Bloch¹⁷ reported more frequent infections in vitamin-A deficient children and Bean and Hodges¹⁸ found more frequent upper respiratory infections in men with *induced* pantothenic acid deficiency. The earliest demonstration of the effect of a specific vitamin deficiency, however, is that of Hess¹⁹⁻²¹ who found children with clinical scurvy to have an increased frequency of diphtheria and of infections such as adenitis, otitis and nephritis. Riddle *et al.*²² have called attention to the frequent occurrence of Staphylococcal, Streptococcal and Vincent's organism infections in the mouth of pellagrous patients which clear up only after riboflavin treatment. Jelliffe²³ reports that suppurative gingivitis of Vincent's type is associated with a 30 per cent mortality in malnourished children.

More field studies are needed of the type reported by Orr and

Gilkes²⁴ who found tuberculosis, rheumatoid arthritis and fatal respiratory infections to be much higher in an African tribe on a predominantly cereal diet than in one consuming considerable milk and meat. When milk, meat and greens were added to the diet of the former, the prevalence of these infections dropped markedly.

Nutrition and Viral Infections. The review article previously mentioned¹ summarizes some fifty studies of the effect of various nutritional deficiencies in the chicken, mouse, rat, guinea pig, rabbit and monkey on a variety of virus disorders, but includes only two references to studies in man. These are the reports of Findlay²⁵ and Hahn and Bugher²⁶ that infectious hepatitis is more severe among undernourished African tribes. Both Vilter and Thompson²⁷ and Franklin *et al.*²⁸ have suggested that dietary deficiency may be harmful in human hepatitis, but provide no substantiating data. Studies in experimental animals indicate that specific vitamin deficiencies are frequently antagonistic to the growth of the virus within the host. Often no effect is detected, but in contrast to other types of infection, synergism of virus infections with nutritional deficiency is the least common finding.

Nutrition and Rickettsial Infections. In rats, deficiencies of vitamin A, thiamine, pantothenic acid, pyridoxine, riboflavin, folic acid, vitamin B₁₂, ascorbic acid and protein deficiency have all been shown to be synergistic with typhus. Despite the assertion that a population feeble and exhausted by famine affords the most favourable ground for the development of a typhus epidemic,²⁹ there are no controlled observations of the effect of nutritional deficiency on a rickettsial infection in man.

Effect of Nutrition on Protozoal Infections. In more than 50 studies of the effect of nutritional deficiencies on protozoan infections in experimental animals,¹ synergism and antagonism were observed with almost equal frequency. Intestinal protozoa, however, were almost uniformly synergistic with malnutrition, while hemoprotozoa were more frequently antagonistic. By far the greater number of studies involved members of the genus *Plasmodium* in such diverse animals as the rat, monkey, mouse, duck, chicken and mosquito. On the basis of these animal studies a milk diet has been tried in human malaria^{30, 31} without effect. Van Veen³² states that among malnourished individuals with malaria in Java during World War II chemotherapy had to be combined with improved diet before satisfactory results were obtained. In Uganda, Góngora and McFie³³ found significantly higher mortality from malaria in malnourished patients.

It was a common experience in prisoner-of-war camps in the Far East during World War II, that severe amoebiasis was particularly associated with periods of acute dietary deprivation but the only published report located is that of Martin and co-workers.³⁴ The studies of Elsdon-Dew³⁵ in South Africa are classical but have not been repeated elsewhere. He found acute fulminating amoebic dysentery common among maize-eating Bantus but rare among curry- and rice-eating Asiatic Indians and Europeans consuming a balanced diet.

Effect of Nutritional Deficiencies on Helminth Infections. Because of the agricultural importance of such observations, a large number of reports have appeared on the effect of malnutrition on helminth infections in lambs and chickens. Similar experimental studies in mice, rats, pigs and dogs have also been reported.³⁶ Sometimes no effect was noted, but in the overwhelming majority of reports the severity of the infection was increased by nutritional deficiency. While it is generally assumed and frequently asserted, on the basis of clinical observations, that this is also true for human populations, controlled observations and direct feeding trials in man are lacking. It has been shown, however, that the production of anaemia by human hookworm infection can be prevented by the administration of iron and in experimental animals, at least, iron therapy also reduces the number of worms.³⁷

Possible Mechanisms of Synergism

1. Interference with Antibody Response. Deficiencies of vitamins A and C and of members of the B complex, in such experimental animals as rats, rabbits and sheep, have been consistently found to interfere with antibody response.¹ Excellent work with dogs depleted by repeated plasmapheresis³⁸ and with rabbits fed extremely low protein diets³⁹ has established that protein deficiency also prevents normal antibody response. Some attempts to demonstrate a similar effect in man, however, have failed⁴⁰⁻⁴² presumably because the protein deficiency studied was not sufficiently severe. In 88 patients with serum albumin values below 4 gm. per 100 ml. Wohl and collaborators⁴³ observed a greatly slowed antibody response to typhoid vaccine. More recently, Olarte and co-workers reported a definite retardation of response to diphtheria antitoxin in 5 two-year-old Mexican children with severe malnutrition.⁴⁴

Budiansky and Da Silva⁴⁵ found that 12 of 15 children with Kwashiorkor showed almost no antibody response to typhoid vaccine as compared with the essentially equal and normal responses of 10

well-nourished controls and 8 children with retarded height and weight, intestinal parasites, anaemia and moderately decreased serum protein, but without oedema or frank clinical signs of vitamin deficiency. There is an obvious need for more studies of the effect of severe malnutrition in humans on the various types of antibody response.

2. Effect on Phagocytic Activity. In experimental animals folic acid and protein deficiencies have been found to interfere with leucocyte response to infection and deficiencies of vitamin A and C to reduce the capacity of leucocytes to phagocytize bacteria.¹ Studies of the effect of the malnutrition on phagocytic activity in man are limited almost entirely to the casual observations of a number of authors that even severe infections may cause no more than a feeble leucocytosis in children with Kwashiorkor.⁴⁶ Hennesy⁴⁷ found no consistent differences in the leucocyte counts of inmates of Uganda jails receiving varying levels of vitamin A intake, but Hassan and co-workers⁴⁸ studying malnourished individuals in the Punjab concluded that higher vitamin-A levels were associated with an increased proportion of lymphocytes and monocytes. Prolonged wasting disease *per se* does not seem to affect the total number of circulating neutrophils.⁴⁹ It is obvious that the effect of nutrition on phagocytosis in man needs further study; such investigations have been limited by unsatisfactory methods, and reliable quantitative procedures are still to be developed.

3. Alteration of Tissue Integrity. Many dietary deficiencies seriously interfere with the integrity of tissues; epithelial surfaces are among the most obviously involved. It has long been assumed that these changes result in a lowering of the resistance of the tissues to bacterial invasion and multiplication. Among the possible alterations are: (a) increased permeability of intestinal and other mucosal surfaces; (b) reduction or absence of mucous secretions; (c) accumulation of cellular debris and mucus to give a more favourable culture medium; (d) alterations in intercellular substance; (e) interference with normal tissue replacement and repair; (f) loss of ciliated epithelium in the respiratory tract; and (g) nutritional oedema with increased fluid in the tissues. There is some evidence from animal studies that some of these alterations are directly involved in the lowering of resistance to infection as a result of malnutrition, particularly with vitamin-A deficiency. While direct experimental confirmation in man is almost wholly lacking, there is no reason to doubt the application of some of the results of animal studies to disease resistance in man.

4. Interference with Non-specific Protective Substances. Quite apart from the protection afforded by the generation of specific antibodies, tissue fluids vary in their capacity to destroy pathogenic organisms. This ability has been shown to be decreased in rachitic rats tested with *Salmonella typhosa*^{50, 51} and staphylococci⁵² as well as in rats deficient in thiamin, riboflavin and vitamin A when challenged with *Salmonella typhimurium*. Nutritional deficiencies have also been shown to interfere with substances which retard the development of intestinal nematodes in rats and horses. In humans these substances have been referred to as lysozymes and reported to be reduced in the tears of children with xerophthalmia,⁵³ the saliva of malnourished patients with cholera⁵⁴ and the bowel wall and secretions of vitamin-A deficient children.⁵⁵ The importance of these observations is difficult to assess until further studies are done.

5. Nonspecific Destruction of Bacterial Toxins. In addition to the destruction of bacterial toxins by specific antibodies, experimental animals with specific nutritional deficiencies sometimes prove more susceptible than controls to toxins such as those from the diphtheria and tetanus organisms, even though there is no detectable difference in the rate of antitoxin production or disappearance of injected toxin. Studies have involved B-complex and vitamin-A deficiencies in rats,^{56, 57} guinea pigs with scurvy^{58, 59} and sheep⁶⁰ and mice⁶¹ on deficient diets, but the phenomenon has apparently never been investigated in man.

6. Reduced Bacteriocidal Activity of the Properdin System. Properdin is a euglobin which occurs in the normal serum of all animals thus far tested and appears to be associated with natural resistance to many diseases of bacterial, viral and even protozoan aetiology.⁶² A technique is now available for its measurement in human serum⁶³ and the influence of various nutritional deficiencies on the properdin system should be investigated. In the only study of this type reported to date⁶⁴ severely malnourished patients with anorexia nervosa had normal properdin levels.

7. Nutritional Alteration of Endocrine Balance. It is well established that the resistance to infection of the patient with severe adrenal cortical deficiency is markedly diminished,^{65, 66} and protein deficiency and probably certain other nutritional deficiencies lower adrenocortical function. On the other hand, Selye⁶⁷ considers malnutrition to be a stress which increases adrenocortical activity as part of the general adaptation syndrome. Despite evidence that cortical hormones may have a direct inhibiting effect on certain bacterial endotoxins^{68, 69} it is very well established that the net

effect of prolonged cortisone therapy is a decreased resistance to infection.⁶⁹

Diabetes is another endocrine disorder in which resistance to infection is notoriously lowered, although Pollack⁷⁰ believes this to be a secondary effect of the huge nitrogen losses which occur during periods of ketosis. It can only be concluded that the relationships among nutritional deficiency, endocrine change and resistance to infection have not been sufficiently explored.

Mechanisms of Antagonism

Antagonism between nutritional deficiency and an infectious agent is almost limited to viruses and the highly parasitic protozoa both of which are totally dependent upon the host cells for their nutritional needs and have very specific requirements for preformed organism molecules. When the nutritional deficiency is sufficiently severe to interfere with key enzyme systems in the host, it is not surprising that multiplication of the virus or protozoa is hindered. There is a great deal of biochemical evidence beyond the scope of this chapter, most of it from studies in experimental animals, indicating that this is the mechanism of antagonism between a nutritional deficiency and an infectious organism wherever it is encountered.

While antagonism has been amply demonstrated in experimental studies, it should be emphasized strongly that it has little, if any, clinical or public health application. This is partly because nutritional deficiencies usually result in antagonism only when the animal is so malnourished as to be almost moribund. Under these circumstances, any advantage to the host in combating a virus, for example, is likely to be more than offset by the adverse effects of the malnutrition. One of the most serious of these is synergism with secondary bacterial complications which are most likely to be the final cause of death in viral diseases.

Influence of Infection on Nutritional Status

Effect on Protein Malnutrition. It is now generally recognized that in a high percentage of cases of Kwashiorkor, the child has experienced an infection some weeks before the actual onset of clinical signs of protein deficiency. This infection superimposed on underlying malnutrition, precipitates the acute syndrome.^{23, 71, 72} While this is an epidemiological observation, metabolic balance studies provide an adequate explanation of this effect. Bacterial infections, including erisipelas,⁷³ meningitis,⁷⁴ malaria,⁷⁵ pneumonia, pyelonephritis, paratyphoid,⁷⁶ typhoid^{77, 88} and tuberculosis have

been shown to produce a negative nitrogen balance. The magnitude of the influence of these infections on nitrogen metabolism is much greater than can be accounted for by an increase in metabolic rate due to fever⁷⁹ and appears to be due primarily to an actual breakdown of cellular protein and urinary loss of nitrogen.

Not only bacterial infections are involved; epidemics of Kwashiorkor 6-8 weeks after an outbreak of measles have been reported.^{80, 81} Recent INCAP metabolic studies in children have shown that chicken-pox considerably increases urinary nitrogen excretion⁸² and that even as mild a viral infection as that induced by the 17D strain of yellow fever vaccine⁸³ has a detectable and consistent adverse effect on nitrogen balance. A further factor accounting for the frequency with which an infection seems to precipitate protein deficiency is the effect of anorexia on the food intake and the custom in many technically underdeveloped areas for the mother and even the physician to place a sick child on a liquid diet without milk or other adequate protein source.

The adverse effect of infection on nutritional status is, of course, not confined to children, even though the young child is most often on a previous diet so poor in protein that the added stress has serious consequences. Certainly some of the consequences of the multiple acute and chronic infections common among people living under unhygienic conditions are a result of their effect on nutritional status rather than a specific manifestation of the infection. The effect of intestinal helminth infections on nutritional status, while probably not as important as formerly supposed, is none the less a contributory cause of many cases of Kwashiorkor.^{84, 85}

Effect on Vitamin and Mineral Metabolism. As early as 1892, Spicer⁸⁶ observed that children in late stages of tuberculosis, meningitis, infantile diarrhoea, and after measles, whooping cough or chicken-pox, often developed xerophthalmia. More recently, Oomen⁸⁷ from experience in Indonesia has emphasized the importance of diarrhoea of infectious origin and measles as frequent precipitating causes of xerophthalmia in Indonesia. This is entirely understandable, since decreases in serum vitamin-A levels have been demonstrated in rats with acute infections such as pneumonia, abscesses and acute rheumatic fever.⁸⁸⁻⁹⁰ Another type of interference with vitamin-A nutriture is the impairment of vitamin-A absorption in children infected with *Giardia lamblia*.^{90a}

Beri-beri⁹¹⁻⁹³ and scurvy⁹⁴ are other vitamin deficiency diseases which are frequently precipitated by acute infections and even vaccination against small-pox has been reported sufficient to induce

the latter⁹⁵ in children with pre-existing deficiency. In investigating the effect of an influenza epidemic on whole blood ascorbic acid levels in Indian school children, Vaishwanar and co-workers⁹⁶ showed that low levels were a result and not a cause of the illness.

Infection may be a major ætiological factor in megaloblastic anæmia in infancy,⁹⁷ and the voracious appetite of *Diphyllbothrium latum*, the fish tape-worm, for vitamin B₁₂ may result in the development of macrocytic anæmia in infected individuals.⁹⁸ May and co-workers⁹⁹ have reported that in monkeys fed a folic-acid-deficient diet, spontaneous infections will precipitate megaloblastic anæmia.

Iron deficiency anæmias may also occur in man as the result of infections.¹⁰⁰⁻¹⁰² The so-called anæmia of infection appears to be due to both a marked inhibition of the bone marrow and a shortening of the erythrocyte life span. The depletion of other minerals especially potassium occasioned by acute diarrhoea may be another serious consequence of infection.¹⁰³

General Considerations

There has been an unfortunate tendency in recent years for nutritionists and clinicians to dismiss the adverse effects of malnutrition on resistance to infection as unproved or unimportant. One reason is that in the highly developed countries where most nutritionists are trained the nutritional status of the population has improved to the point where malnutrition severe enough to influence the course of an infection is rare. Under these circumstances, the short-term effects on nutritional status of acute infection are not of serious consequences. Where both malnutrition and infection are serious public health problems, as they are in most tropical and technically underdeveloped countries, these interrelationships assume great importance and indeed, success in the control of either problem may depend on progress towards solving the other. The widespread occurrence of Kwashiorkor is a reminder that nutritionist and clinician must recognize that in many areas of the world today malnutrition of such severity as to affect resistance to infection is common especially among young children.

The spectacular and apparently contradictory occurrence of antagonism in the relationship between the experimental deficiency of specific nutrients and many of the viruses must not be taken as an argument against the importance of synergism in the interrelationships between malnutrition and resistance to bacterial, rickettsial and helminth as well as some viral and protozoan infections. Nor should the inadequacy and empirical nature of many of the studies of

nutrition and infection, particularly those which are clinical or epidemiological, be allowed to obscure the tremendous number of convincing and worthwhile studies which clearly indicate the importance of nutrition in resistance to infection. Because of the fact that most of these deal with experimental and domestic animals rather than man, their implications have often not been sufficiently appreciated by clinicians and public health workers.

It should also be emphasized that even where antagonism between the deficiency of a nutrient and of a specific infectious agent exists, the deficiency is likely to lead to disastrous secondary complications. At the opposite extreme much harm has been done by the excessive claims which have been made in the past and are sometimes still made today for the value of therapeutic doses of vitamins in preventing or ameliorating infections. The resulting abuses in vitamin administration and the lack of result when vitamin supplements are added to an already adequate diet are partially responsible for the reaction against the whole concept of nutrition as an important influence on the course of infections. Medical practice must not be carried beyond scientific evidence, and there is no basis for believing that high doses of vitamins will be more effective in contributing to optimum resistance to infection than an adequate diet.

There has also been some tendency to misinterpret experimental studies in which dietary variations were superimposed on extreme genetic variations in host resistance and agent virulence. In the classical work of Schneider¹⁰⁴ a deficient diet had little effect on the mortality of rats when either highly susceptible or highly resistant rat strains, and either highly virulent or relatively avirulent *Salmonella* were employed. When strains of rats with intermediate resistance, however, were exposed to *Salmonella* of moderate virulence, mortality was greatly increased by an inadequate diet. As Schneider himself has emphasized, this is the type of situation found most commonly in nature and the complete experiment is a strong argument for the practical importance of nutrition as a factor influencing resistance to infection.

A word of caution is required on the use of terms. Some authors have attempted to distinguish "susceptibility factors", which decrease the extent or effect of infections when they are withheld, from "resistance factors" which lead to an increase in the infection when they are deficient in the diet. To avoid confusion the term "susceptibility" has not been used in this discussion and the above two concepts have been expressed by referring to either an increase or a decrease in resistance. Another type of distinction should be

made; there is a difference between the simple infection of the host by the agent and the development of disease as a result of this infection. While the term resistance has been used to refer to biological barriers to either infection or infectious disease, it is probable that most synergism involves the consequences of infection, i.e. the development of disease, rather than the initial invasion of the body by a potentially pathogenic organism.

From the foregoing discussion, it is evident that nutrition may influence infection in a number of different ways. Consequently, the demonstration that a given deficiency is not exerting influence on some particular one of these is no assurance that it is without effect. Furthermore, nutritional deficiency may conceivably augment infections by either (a) acting on the host to facilitate initial invasion, (b) influencing one or more of the several defense mechanisms of the host, (c) favouring secondary infection, or (d) retarding convalescence after the acute phase. The better-controlled experimental studies have been confined mainly to attempts to evaluate resistance by measuring the ability of the host to produce antibodies. Future investigations of the effect of nutrition should explore the sum total of body mechanisms which influence the development of infectious disease.

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CHAPTER 30

CARDIOPATHY OF UNKNOWN ORIGIN IN AFRICA

by

J. G. THOMSON

IN recent years no less than three named and apparently distinct types of unusual heart disease have been described from Africa, largely on the basis of pathological findings at autopsy, though differences in clinical behaviour have been mentioned. They appear to have a regional distribution; endomyocardial fibrosis from Uganda^{3, 4} and from Johannesburg, nutritional heart⁷ and cardiovascular collagenosis with parietal endocardial thrombosis.² These three types have been put forward as distinct entities, with little or no overlap in any one region. Yet in the last 12 years in the autopsy service of the Medical School of the University of Cape Town we have encountered examples of all three types in the Bantu and Coloured, and exceptionally in Europeans. On this experience and on reading the literature on the subject, we believe that the morphological resemblances between them are much greater and more significant than the described differences, much of which appears to be the result of selection, and of different views on ætiology and pathogenesis.

Gray⁶ has shown that similar conditions have been intermittently described as rarities in the literature from 1901 onwards, but the recording of large numbers of similar cases and the giving of special names is of comparatively recent date. It would appear that the three named cardiac lesions are accepted as distinct and unrelated morphological entities, and the purpose of this communication is to stress that this is not so as regards two of the named lesions in the current opinion of the pathologists who first described and named them, and to give grounds for the opinion that the third is a variation on the same morphological theme.

It is not suggested that this morphological similarity in any way implies a uniform ætiology or pathogenesis. The extent to which the myocardium can show morphological or histological changes as the result of disease is limited, and complications and sequelæ such as thrombosis or fibrosis are equally limited. Indeed, it might be wiser

at the moment to accept that, as in the kidney and liver, there may be more striking differences between the chronological stages or intensities of a single disease process than there are between the fibrosed end-results of quite different disease processes.

It should be stressed initially that diagnosis of these obscure heart conditions can be established only at autopsy. Clinically it is suspected largely on the basis of exclusion of other causes of congestive heart failure, but even in Uganda where atrioventricular valvular involvement has been stressed, Shaper and Williams¹⁰ indicate that half of their proven autopsy cases had no valvular involvement, and that syphilitic cardiovascular disease, still common in that area, was found at autopsy in patients who had been fully investigated during repeated admissions and clinically diagnosed as arteriosclerotic/degenerative heart disease or endomyocardial fibrosis.

From the point of view of the relationship of these three named cardiac conditions to one another, the most important article is the report of a seminar at the University of the Witwatersrand in 1957¹¹ where the three pathologists who had described and named these heart lesions met and discussed the matter together.

In the discussion that followed the description of endomyocardial fibrosis,^{3, 4} nutritional heart⁷ and cardiovascular collagenosis,² Higginson agreed that the differences between nutritional heart (N.H.) and cardiovascular collagenosis (C.V.C.) were differences of interpretation. On his part, Becker agreed that the two conditions N.H. and C.V.C. were essentially the same, and that he and Higginson "differed only in pathogenesis and interpretation". Further evidence was given that the described clinical differences between the two conditions were less than originally stated. We can but accept the present opinion of Higginson and Becker that N.H. and C.V.C. are different names for the same morphological condition. Both stated that they had encountered cases corresponding to that of E.M.F.; "the very occasional case"⁷ and "very rarely"⁷, but both were referring to the more extreme type of E.M.F.

Davies, however, did not see any relationship between the disease described by him and those described by Higginson and Becker; nor did he accept the opinion of these two authors that N.H. and C.V.C. were essentially the same. He admitted that it was possible that they had in Uganda some examples similar to those of C.V.C. among their unexplained heart cases, but rejected the view that E.M.F. was a late stage of C.V.C. or N.H., as these were uncommon in Uganda. He stressed the rarity of embolic phenomena in E.M.F. and its high frequency in N.H. and C.V.C.

Some of this may well be based on selection of cases. Davies reported in the seminar that in Uganda 30 per cent of cases of heart failure could not be given a conventional clinical diagnosis. At autopsy one-half of these are regarded as E.M.F. and an equal number are not. Two-thirds of the last are described as hearts with endocardial thickening or mural thrombosis, half of them associated with cirrhosis of the liver or other form of liver disease. No details, unfortunately, are given of this large group of cases of heart failure of unknown origin, amounting to two-thirds the number of E.M.F. cases, and most pathologists in South Africa would put many if not most of them in the group of cardiopathy of unknown origin. By inference, none of these would have shown the described features of E.M.F., though endocardial thickening or mural thrombi are present, and it is difficult to avoid concluding that this is, in part at least, the reason for the differences between obscure myocardial disease in Uganda and in South Africa. A two-third dilution of the more severe E.M.F. types by less marked examples would put the average nearer to that seen in South Africa.

This selection may also be a factor in the relative infrequency of embolic phenomena in E.M.F., which is variously recorded as 3 out of 36 cases³, "embolic lesions have not been common in our (20) cases"² and "rarely seen in the cases in Uganda (comprising well over 100 autopsies), save such as are either due to a terminal bacterial endocarditis, or are *massive terminal infarctions involving major blood vessels*."⁴ The last reservation makes it impossible to assess just how rare embolic phenomena are in E.M.F., but presumably it is less frequent than in the cases from Johannesburg. We have no data on the cases of heart failure of unknown cause in the Uganda series not included in the E.M.F. group, and these, amounting to two-thirds of the E.M.F. cases, might raise the incidence of embolic lesions in all cases of cardiopathy of unknown cause, or else confirm that these Uganda natives show less embolism anyhow, whether the endocardial thrombotic lesions be described as E.M.F. or not. Under these circumstances we do not regard the low or absent rate of embolization in E.M.F. in Uganda as being a significant point of differentiation from heart failure of unknown cause in the Union.

On a similar basis one can suggest grounds for reducing some of the other claimed differences between E.M.F. and cardiopathy of uncertain origin in South Africa, but it is clear that the Uganda E.M.F. cases show a much higher proportion of more extensive endocardial lesions, particularly those extending to involve the atrioventricular valves. Some of this is presumably due to more

careful examination and evaluation of these valvular lesions, or to an altered selection of what cases should be labelled E.M.F. or both. Davies originally in 1948³ recorded in 36 cases only 3 such lesions, 2 tricuspid and 1 mitral, but in 1955 he reported involvement of no less than 25 mitral and 23 tricuspid valves in 32 cases.⁵ In a few years the incidence has been multiplied 18-fold, and the difference between the recorded frequency of valvular involvement in the two Uganda series of E.M.F. by the same author, is probably less than the difference between the Johannesburg cases of Becker and 1955 series of Davies and Ball.

We feel that while some differences remain between E.M.F. and the cardiopathies of South Africa, they are largely quantitative and not qualitative. Depending on whether one takes all the cases of cardiopathy of uncertain origin, as in the Johannesburg cases and presumably in the 1948 series of Davies, or selects some with marked morphological features as in the Davies 1955 series, so will the reports vary.

At this stage we do not think there is enough evidence to justify their being regarded as basically distinct and separate diseases from the morphological point of view, and at the moment the grounds for diagnosis are entirely morphological.

With the exception of Laurie, *et al.*⁸ who state that cardiopathy of uncertain origin consists largely of undiagnosed examples of well-recognized causes of heart disease, notably coronary heart disease, decompensated hypertension and pericardial disease, all workers in Africa on this subject will agree that the lesion or lesions are common and distinctive and that the ætiology or ætiologies are uniformly obscure.

The search for ætiological factors in C.U.O. is handicapped by three major difficulties. First we have the reluctance of pathologists to concern themselves with those cases of obscure heart disease, clinically similar to those under discussion, but which at autopsy merely show large dilated hearts, with minimal thrombi or endocardial thickening or none at all. They constitute at least one-third of the cases of C.U.O. in Cape Town, and appear to amount to two-fifths of the Uganda cases of obscure heart disease.¹¹ Microscopical examination of the myocardium shows changes similar to those of E.M.F., N.H. and C.V.C., to which one would add a constant and striking dilation of the capillaries but with slight or absent endocardial and thrombotic changes. Unimpressive and disappointing, both to the naked-eye and microscopically, these hearts suffer by comparison with the others, and tend to be put aside or ignored.

Yet they are associated with a similar degree of cardiac failure, and constitute a major proportion of heart disease of unknown ætiology. They may be earlier stages of these named cardiac conditions, as I believe they are, but acceptable proof of this is not at present available and they remain neglected. If recent thrombi are present in the hearts they may be morphologically identical with those in beriberi, yet the response to specific therapy is usually absent, and again they are put aside as not conforming to any named cardiac state.

The second factor is the natural desire to search in all cases in any one series for a single uniform ætiological agent. This implies a reluctance to accept that different ætiological factors may produce a similar morphological picture in the heart and similar clinical features. Because of this, individual cases in any one series with an indisputable background of malnutrition may be swamped by the average nutritional state of the group as a whole. For example, O'Brien⁹ mentions 25 cases of endocardial fibrosis, and describes 7. He states that undernutrition and malnutrition were not present in his cases, but only 2 were proven examples and submitted to autopsy. One of these is described as having a diet which was probably deficient, and the other, on a full diet, had cirrhosis of the liver. In the same way there were 3 cases of cardiopathy of uncertain origin in Europeans in the autopsy service of this Medical School in 1952, a very abnormal number and more than we have had in the 8 years since. All 3 were chronic alcoholics, 1 a bromide addict in addition, and 2 showed cirrhosis of the liver. The 2 with cirrhosis of the liver showed signs of both malnutrition and undernutrition, while the third was well-covered and free from signs of malnutrition. All 3 had large dilated hearts, but only 1 had endocardial fibrosis and organizing mural thrombi.

It is easy to say and believe that in one of these cases malnutrition played no part in the ætiology of his heart disease; it is just as easy to conclude that in the other 2 cases deficiencies may well have been responsible, entirely or to a major extent, but neither of these opinions can be based on evidence which would be accepted as proof.

It is difficult at the moment to see how proof of presence or absence of nutritional deficiencies is to be obtained. Diseases due to vitamin deficiencies are often characterized by a rapid and uniform cure when the deficiency is made good, and consequently, when no such benefit follows the administration of individual vitamins, the conclusion is reached that the disease or symptoms are not the result of deficiency of these vitamins. But even if this conclusion

were entirely warranted in vitamin deficiencies, it does not always apply to deficiencies of proteins and amino acids, which may result in irreversible changes in the target organs and a failure to produce a cure when the deficiencies are corrected. A marked degree of fibrosis of the endocardium is clearly an irreversible process, however produced, and one which will interfere with cardiac function. It may well be that some cases of C.U.O. are indeed due to malnutrition, and may go on to a fatal outcome, even if the missing food factors are given in adequate amounts. This, however, is no ground for not attempting similar therapy in other apparently similar cases, as at the moment the demonstration of food deficiencies as a cause of C.U.O. would seem possible only by substitution therapy effecting a cure. A few such positive cases, adequately documented, are not neutralized by many negative ones, even if all cases of C.U.O. were the result of dietary deficiencies, or of the same dietary deficiencies. Until disproved it would seem more profitable to presume that more than one ætiological factor may be responsible, and to consider precise ætiological factors only in individual cases of C.U.O.

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CHAPTER 31

TRENDS IN NUTRITION IN THE FRENCH-SPEAKING COUNTRIES

by

J. TREMOLIÈRES

GENERAL TRENDS AND THE PRESENT OUTLOOK

THERE is a growing interest in clinical nutrition in French-speaking countries, but this interest is still mainly "platonic", very few clinical groups having a structure which allows for research.

This growing interest has different origins. Ordinary physicians are acquiring greater experience of the dangers of many drugs and of their dubious usefulness in many chronic diseases such as cirrhosis, arteriosclerosis, undernutrition, obesity and mental disturbances. Hippocratic "dieta" depending on the "good way of living", including food, rest and philosophy of life, is needed more and more in the overloaded and often meaningless activities of modern life; these appear less and less to constitute civilization as distinct from slavery ordered by technocracy.

University physicians are increasingly aware that the physiological, cellular and biochemical foundations of nutrition are the common denominator of pharmacology, toxicology, metabolic bases of diseases and endocrinology.

Public health officers who have visited Anglo-Saxon countries and have heard something about the role of nutrition in health, have begun to think that Public Health may mean rather more than sanitation.

As regards "Professors" of the basic medical sciences, the position is generally less favourable. Being fundamentalists and theorists, they have a feeling that nutrition consists in cooking; manual labour is not the business of "academicians" whose interests sometimes do not extend beyond the confines of the university.

But two economic facts are responsible for these evolutionary trends. France, which was, and still is, the country where there is a different cheese and a different wine for each day of the year, which is the country where "coquetterie" and "gourmandise" (two words with no English equivalent) originated, is rapidly industrializing its

food production. Food is no longer the product of the agriculturist's art, a flower of national traditions. It is now scientifically produced and uniform in taste and quality. This change is creating a kind of anxiety, and people want to know more about these "unnatural foods". This anxiety is strong enough to affect public opinion. Manufacturers themselves are starting to raise questions about the effect of what they are doing on health. The second economic fact is the transformation of the social aspects of the hospitals. As A. Camus⁶ has pointed out, in our modern cities and in our busy life, there is no room for the sick, the crippled and the dying. They must be in hospitals. To meet public demand the hospital is more and more luxurious. Food is one factor contributing to this comfort. Administrators are ready to spend money on dietitians.

All these feelings, opinions and economic trends have yet to culminate in real achievement. In the Public Health Departments of France, Morocco, Tunisia, Mali, South Viet Nam and Madagascar, there are Nutrition Sections consisting of either a single man or a laboratory or a team concerned with nutrition surveys. In France two schools for dietitians were inaugurated within 10 years; in Belgium one. Eight years ago the "Association des Diététiciennes de Langue Française" was formed which now has about 300 active members and its own review. Medical schools have lagged behind. They have no official teaching in nutrition, but during the last 4 years personal initiative has succeeded in organizing in Paris co-ordinated teaching in physiology, biochemistry and clinical and applied nutrition.

The main difficulty is probably to decide on the kind of men and of research organization needed to constitute a human nutrition laboratory. Clinical nutrition needs fundamentally the effective co-ordination of much of the fields of biology, medicine and hygiene. Latin individualism acts as both bridle and safeguard in the development of such groups. Some have started, the oldest being 20 years of age.

SPECIFIC TRENDS

We have included under "clinical nutrition" conditions in which the diet is either a cause or a treatment of a disease or in which the metabolic aspects of relations between diet and disease are important.

Liver Cirrhosis

Cirrhotogenic Diet. In France alcoholic cirrhosis constituted 77 per cent for men and 70 per cent for women of the total cases of

cirrhosis in 1950-51. These percentages are based on mortality data. From morbidity figures in different hospitals figures of from 80 to 99 per cent are given (Lederman²¹). The death rate from cirrhosis rises in correlation with wine consumption. This is true at the national level and, as is shown by a more detailed analysis, also for different socio-economic groups. For instance, in the city of Marseilles, the cirrhosis mortality incidence index is 0.74 among non-manual male workers with an average wine consumption of 689 ml. and the same index is 1.36 among manual workers with an average wine consumption of 962 ml.

An interesting fact quoted in these surveys is that tobacco consumption is in close correlation with wine consumption (Bresard⁴).

From a careful and extensive survey it appears that ordinary wine is responsible for about 80 per cent of alcoholic cirrhosis, and that the cirrhogenic diet has two characteristics: (1) the consumption of over 1 litre a day (10 per cent) of wine for men and of over 0.750 litre a day for women; (2) a reduction of the non-alcoholic calories and protein which, in the beginning, is small (< 20 per cent) and then increases, reaching 50 per cent during the last 8 to 6 months before the full evolution of the disease (J. Tremolières²³ (Fig. 1); G. Pequignot²⁶).

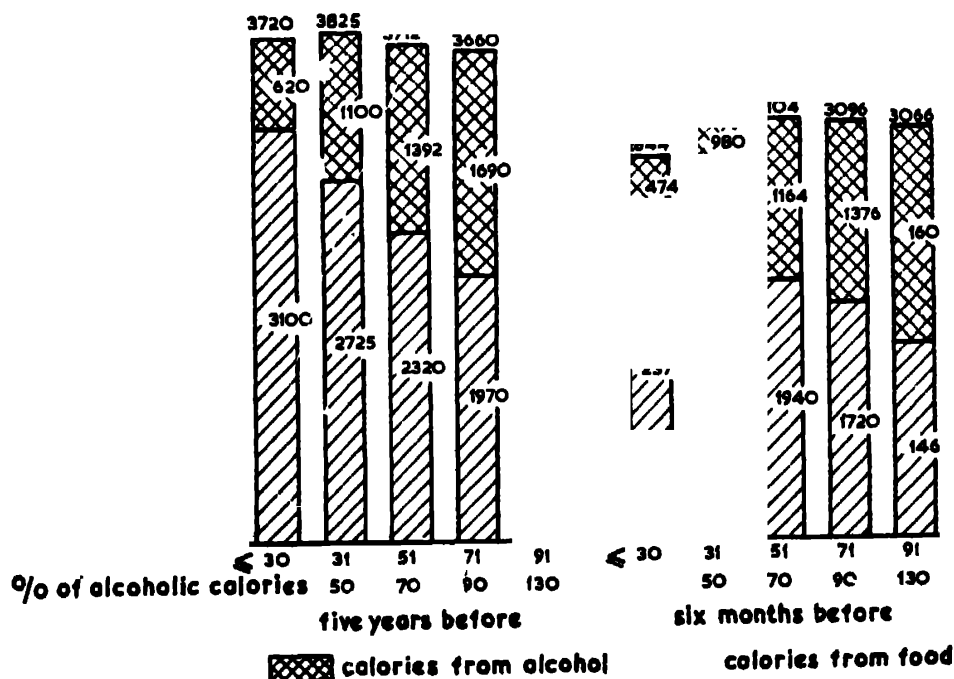


FIG. 1. Calories from alcohol [Cross-hatched] and from food [Diagonal lines] in 32 cirrhotic in Paris. J. Tremolières *et al.*²³.

TABLE 1

Distribution of Wine Consumption among 116 Male Cases of Alcoholic Liver Cirrhosis and 116 Controls (same age)

(G. Pequignot)

Wine (10%) Consumption (l./day)*	Alcoholic cirrhosis No. of cases	Controls (same age)
< 1 litre	1	59
1 to 2 litres	51	50
> 2 litres	64	7

* Total alcohol consumption expressed in wine (10 per cent). In practice about 80 per cent of alcohol consumption was wine.

Undernutrition in Alcoholic Cirrhosis. From nitrogen, sodium and potassium balance studies, J. Tremolières *et al.*³³ concluded that alcoholic cirrhosis patients are more severely depleted of protein than any they had ever seen. They are able to store between 5 to 10 g. of nitrogen per day for 2 months on a diet of 20 g./N/day.

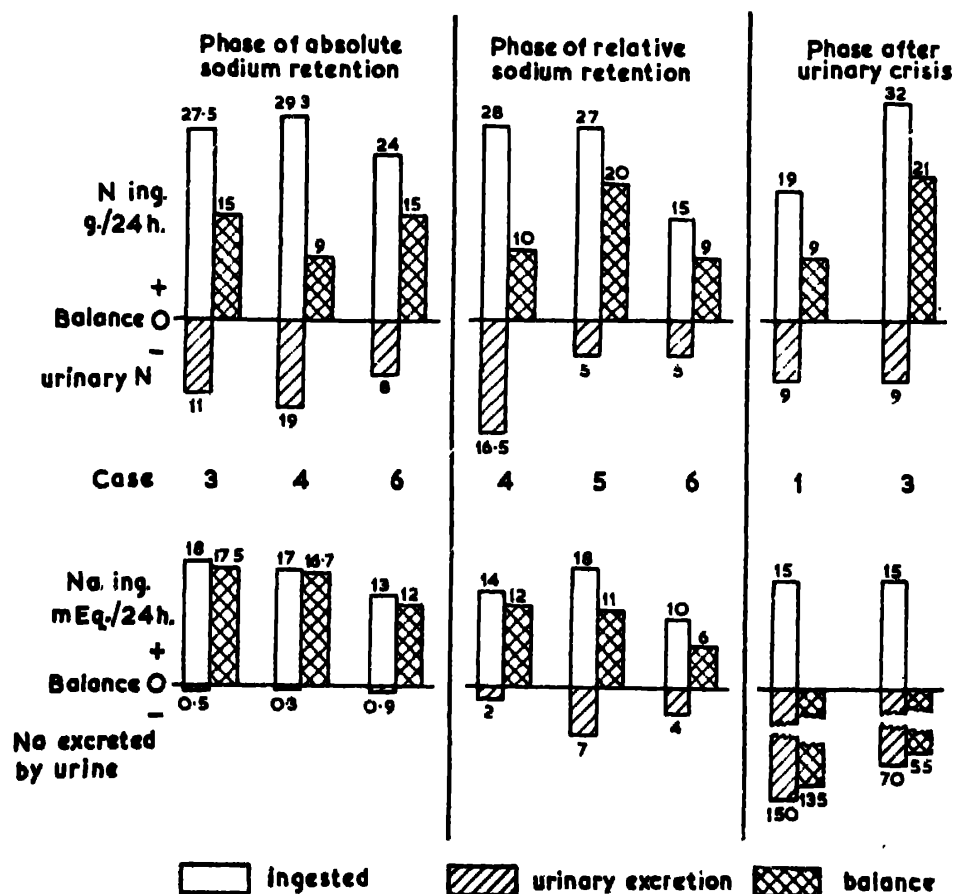


FIG. 2. Nitrogen and sodium balances in alcoholic cirrhosis—(mode values; among 7 cases). J. Tremolières *et al.*³³.

Sodium excretion is less than 1 mEq./day, during the fully evolved stage. Therefore the diet must be as low as possible in sodium. In spite of a low sodium diet, however, the reproduction of ascitic fluid is often greater than would be expected from sodium balance. Serum sodium is often low (120–135 mEq./l.) and is not corrected by giving sodium but paradoxically by a high-protein low-sodium diet.

The ascitic fluid is a compartment where diffusion of labelled Na, K and alcohol is generally very slow, 2 to 3 hours being necessary for the equilibration with the plasma level (Cl. Sautier³²).

L. Carre⁸ has shown that the diffusion space of alcohol in alcoholics and cirrhotic patients is greatly reduced. The curves of alcoholæmia are far from being a straight line. Therefore the coefficient of ethyl oxidization (CEO) cannot be calculated correctly from alcoholæmia in these cases.

Caroli *et al.*⁷ observed 95 cases of cirrhosis on a high-protein diet (1.2 to 1.5 g./kg.) excluding alcohol completely, for a period of 27 months. Thirty cases were still living without ascitic fluid and tolerating sodium. Twenty-seven were considered well established. When combined with streptomycin this diet is well tolerated and hyperammonæmia is exceptional. In cases with previous hæmorrhages, it is dangerous to give more than 1 g./kg. of protein.

Chronic Toxicity of Alcohol. The previous data on undernutrition and on food suggest that in alcoholics alcohol, instead of having its classical protein-sparing action, can lead to wastage of nitrogen. In this context, L. Carre⁸ observed that in alcoholics, ethanol has a specific dynamic action of 47 per cent (10 subjects). In alcoholics and cirrhotics, alcohol oxidation is accompanied by an increase of plasma non-protein nitrogen. This could be explained if the peroxidase-catalase system of Keelin and Hartree were to operate in alcoholics.

In the same context, Griffaton *et al.*¹⁶ in their work on rat liver homogenates observed that ATP increased alcohol oxidation, and that agents which block xanthine oxidase inhibit alcohol oxidation under these conditions.

It is therefore possible that the nitrogen-wasting effect of alcohol observed in cirrhosis might be due to oxidation through a peroxidase-catalase system using adenosine or D-amino acids, this pathway suggesting one possible explanation for the chronic toxicity of alcohol.

Physiological Conditions of Ethanol Oxidation. The work of Le Breton²⁰ had demonstrated that ethanol is oxidized, although only at basal metabolic conditions, up to about 50 per cent of expenditure without SDA, and that CEO is not raised by cold environment or

muscular work. In confirmation of this Dontcheff,¹³ working on rats, frogs and yeast cells, found that the ratio of calories from alcohol oxidation to caloric expenditure at basal metabolic rate is 0.5. This figure can be raised up to 0.7 by a diet rich in protein and carbohydrate or insulin, and is lowered to 0.3 by fasting or a lipid diet.

Practical Conclusions. Cirrhosis of the liver appears to be frequent among men drinking more than 1 litre of wine and women more than 0.750 litre (10 per cent). These patients are more severely protein-depleted than can be predicted from their reduction of food intake. It is possible that an abnormal ethanol oxidation through a peroxidase system might be one explanation for the chronic toxicity of alcohol.

To prevent the disease it is recommended that wine consumption should never exceed 1 litre for men and 0.750 for women. Alcohol consumption is more dangerous if food is correspondingly reduced.

To stabilize the disease, complete exclusion of alcohol, high protein (1.2 to 1.5 g. protein/kg.) and low salt (< 300 mg./Na/day) is recommended, associated with antibiotics to avoid ammonæmia. A high-protein diet is dangerous in cases where there has been hæmorrhage.

Kwashiorkor and Pellagra

Dupin¹⁴ made an extensive study of 563 cases of kwashiorkor hospitalized in Dakar during a period of 5 years. Eighty-five per cent of his cases were between the ages of 1 and 3 years. Diarrhoea and anorexia were the first signs. In 200 X-rays no bone alterations were seen. Bone maturation was normal except in 10 per cent of cases where there existed a slight retardation. The average total plasma protein on admission was 4.2 g. per cent (460 specimens albumin, 14.3 g./litre; α 1 globulin, 4.0; α 2 globulin, 6.5; β globulin, 5.1; γ globulin, 14). Serum sodium is often low (average 132 mEq.) and serum potassium too (3.3 mEq./l.). Amylase is low (5 to 10 Somogyi units), hæmoglobin is nearly normal (12.059). Liver biopsies showed that at first the steatosis is periportal; the intensity of the steatosis is not proportional to the severity of the case. The mesenchyme is generally normal. In about 30 per cent of cases a portal fibrosis was noted. Electronic microscopy showed a cloudy swelling of mitochondria, with a reduction of the ergastoplasm. During protein refeeding, ergastoplasm appeared very dense around the mitochondria which reappeared normally.

Intestinal parasites were observed in about 65 per cent of cases, mainly ascarides (18 per cent).

A new form of infant protein malnutrition was described by Paque²⁵ in Morocco. The increased consumption of sweet tea without salt in summer produces a water intoxication with polyuria, œdema and vomiting. In protein-depleted children, plasma sodium is low. Complete water deprivation for 2 to 4 days cures the acute phase.

Mitrovic²⁴ kept 30 cases of pellagra on a pellagragenic diet. The diet of one group was supplemented by 500 g./day of potatoes and that of the other by 200 g./day of wheat flour. Symptoms disappeared in 49 per cent of those on potatoes; wheat had no effect. In this same context Tremolières³⁶ observed that different starches interfere in different ways with the action of pepsin and trypsin. Sautier³¹ has observed that starches are like ion exchange resins. Potato starch can pick up ten times more cations than wheat starch, which in turn takes up more than manioc starch. It is possible that this can explain variable anti-peptic or antitryptic effects.

Amylolysis depends on the methods used in the preparation of starches. Perisse²⁷ observed that uncooked manioc starch is hydrolyzed 3 times more slowly than "gary" and 4 times more slowly than cooked starch. These facts draw attention to the old "starch dyspepsia", starch being able to lessen proteolysis, thus increasing protein depletion.

Undernutrition after Gastrectomy

A survey on food consumption (S. Bonfils *et al.*³) and a metabolic study of rehabilitation diets (J. Tremolières *et al.*³⁴) have shown in 20 cases out of 25 patients that caloric and nitrogen intake was reduced to 50 per cent of requirement for habitual weight and that the actual loss of weight (—23 per cent) was of an order that can be calculated from the caloric deficit. The gain in weight followed the normal pattern of simple undernutrition. The digestibility is at the lowest limit of normality, i.e. 1.6 g. of N per 24 hours in 16 cases and 2.2 in 8 cases, the normal being 1.1 g./day. The dumping syndrome in most of the cases was cured at the same time as the undernutrition.

But, in some cases, undernutrition was not only due to dietary deficit. Some cases were "constitutionally thin" and required extremely high caloric levels to maintain normal weight. Some had chronic diarrhoea with reduced powers of digestion.

A re-educative diet given in 4 or 5 small meals rich in animal protein, avoiding milk, is the best preventive.

Parenteral Feeding, Protein Requirement in Catabolic States, Physiological Aspects of Catabolic States

The metabolic utilization of protein and amino-acids given by vein and measured by nitrogen balance is dependent on numerous factors; the importance of caloric and nitrogen deficit in the days and months before the study, catabolic or anabolic condition at the time, caloric intake, type of sugar, of peptides, of Maillard reaction compounds. Denoix, *et al.*¹² observed that, in the catabolic state, the optimal nitrogen intake is about 0.6 g. of protides/kg./day. Below this level nitrogen balance becomes strongly negative; above this level, the nitrogen output rises.

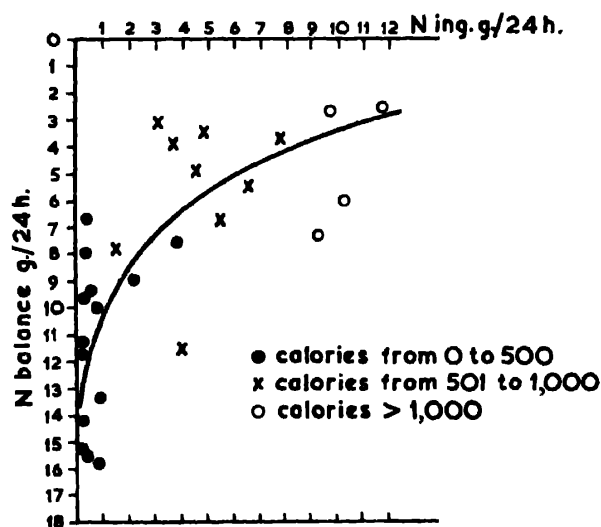


FIG. 3. Nitrogen balance related to N intake in the 10 days following gastrectomy (15 cases) or rectal ablation (12 cases). P. Denoix.

In this state the biological value of a mixture of D.L. essential amino-acids with 50 per cent glycine given by vein (6 g. N/day) is nearly the same as that of milk or meat protein given at the same level by mouth. A sparing effect of 60 to 80 per cent of injected nitrogen on the nitrogen pool of the body is possible with a caloric level of about 500 cal./day (Tremolières³⁷).

The good metabolic utilization of the above mixture of D.L. amino-acids with 50 per cent glycine affects the question discussed by Allison,¹ Holt,¹⁷ of the relative biological value of protein in different metabolic states. The metabolic utilization of such a D.L. mixture raises other questions. De Gasquet and Lowy¹¹ demonstrated in rat kidney homogenates the inversion of D-valine, D-phenylalanine,

D-methionine, D-tryptophan, D-isoleucine, through the keto-acid and the regulation exerted by ATP/ADP/AMP ratios on oxidative deamination and transamination of the D derivatives; thus at a cellular level a mechanism is in sight which could regulate biological utilization of amino-acids.

Azerad² showed the metabolic utilization of perfused human plasma albumin in cirrhosis.

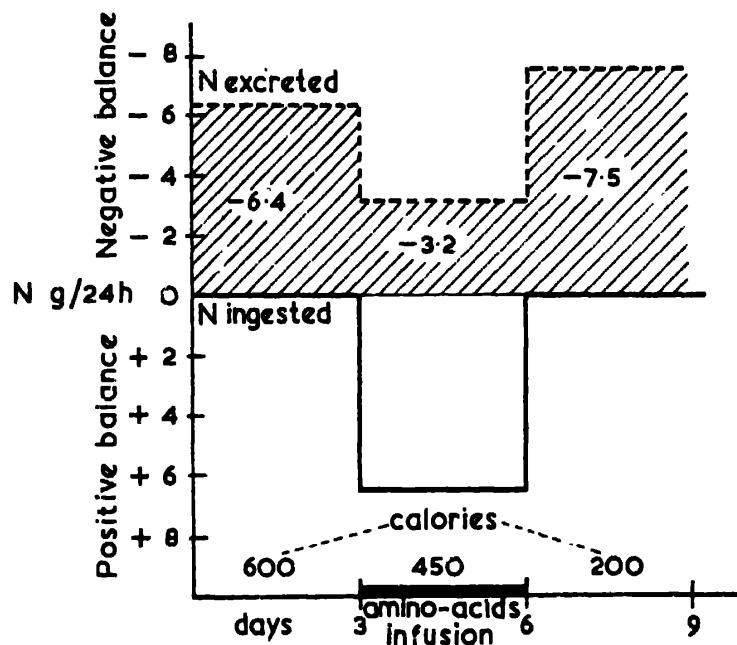


FIG. 4. Effect on nitrogen balance of 6.35 g/24 h nitrogen (mixture of eight essentials D.L. amino-acids with 50 per cent glycine) by intravenous infusion. (Severe catabolic state—Average of 3 cases). J. Tremolières³⁷.

Studying the catabolic phase on cortisone-treated adrenalectomized rats, Tremolières³⁸ observed that the nitrogen catabolism resulted in the destruction of certain protein (lymphoid tissues, muscle) and the synthesis of liver protein, the negative balance being the result of this transfer. This effect is dependent on the reduced level of ribonucleic acids (RNA) in muscles produced by cortisone and of an elevated level in the liver. Such a metabolic state can explain the variability in the utilization and biological value of amino-acid mixtures when compared with a normal or anabolic state. The words "catabolic" and "anabolic" are confusing, catabolism not being shared by all tissues but the result of a change in body structure of which the physiological meaning is still unknown (Tremolières *et al.*³⁸).

Arterial Atherosclerosis

From one dietary survey it appears that, in about 6 out of 10 cases of myocardial infarction, the customary diet shows an excess of 30 per cent in the case of calories and plus 43 per cent and 38 per cent respectively in the case of animal fats and proteins, when compared with the customary diet of control subjects. Transferring an exaggerated form of this diet to male rats (66 per cent of calories from lipids (lard) and 22 per cent from proteins and with high caloric consumption), Tremolières *et al.*³⁵ were able to produce atheroma and arteriosclerosis. The plasma cholesterol is nearly normal if the diet has no cholesterol, and up to four times normal if the diet is supplemented by 2 per cent cholesterol. Aortic and arterial lesions appeared in both cases, whatever the plasma cholesterol.

After 6 months a sudanophilic infiltration of aortic intima appeared and after 10 to 12 months atheromatous chondroid plates with calcium deposits. In the kidney there was fat embolus.

Jacquot *et al.*^{18, 19} observed that rats fed the above diet, one group lard, another sunflower oil or poppy oil, have reserve fats with 7 per cent of linoleic acid in the first case and 45 per cent in the second case. During partial starvation (—75 per cent) and total starvation, the RQ of the first group falls to 0.73 and 0.71 indicating an important mobilization and utilization of reserve fats. The second group has an RQ which does not fall with the reduction in the diet and falls only to 0.74 during starvation, the total oxygen consumption being lowered. This is interpreted as meaning that fats rich in essential fatty acids (EFA) are less mobilizable than saturated ones. This could explain the lower lipæmia observed.

The same group of workers observed an hyperthyroid effect of fatty acid peroxides, and a toxicity of some polymers in the rat (Raulin *et al.*²⁸).

S. Ferret¹⁵ showed that the skin lesions of Burr and Burr's disease do not appear if the diet is rich enough in pyridoxine. Feeding rats with a high level of linolenic acid, she finds this acid neither in the liver nor in the brain. She concludes that linolenic acid is not an essential fatty acid. In a diet lacking in EFA she found no changes in the EFA content of the brain.

These studies suggest that arteriosclerosis is often associated with overeating and a high consumption of animal products with therefore high animal lipid and protein consumption. Feeding fats with high EFA content gives reserve fats less readily mobilizable than produced by more saturated fats. This might explain some aspects

of the hypolipæmic effect of a diet as low as possible in non-essential fatty acids and overloaded with EFA. The National Hygiene Institute recommends that the average human diet should not exceed 35 per cent of lipid calories. The danger of alteration of unsaturated fats, i.e. peroxides and polymers, is pointed out.

J. Loeper²² observed that the silica content of the aorta is greatly reduced in atheroma, both in men and in rabbits, with a certain degree of experimental atheroma in the latter being prevented by a high silica intake in this animal.

Caloric and Nitrogen Expenditure in Obesity

T. Cahn *et al.*⁵ observed in rabbits that the total caloric expenditure is proportional to caloric intake over a large range. Their analyses show that hormones are implicated in this excessive consumption.

The opposite condition was studied by Tremolières *et al.*⁴² who estimate total caloric expenditure over a 2 months period in 29 cases of "constitutional" obesity with the assumption that the loss of 1 kg. of weight cannot give more than 9,000 calories and give figures of 26.2 cal./kg.day for the first month and 21 cal./kg./day in the second month for a sedentary life in hospital. This type of obesity appears as an over-reduction in expenditure when intakes are reduced.

Nitrogen output is not reduced in the same proportion. Negative nitrogen balances were observed when protein intake was below 50 g./day, therefore it seems dangerous to give a reducing diet in which it is below this level.

Digestibility

Method. A method using differential centrifugation makes it possible to separate 5 fractions from human faeces: big cellulose residues, free lipids, very thin cellulose residues, bacteria, water-

TABLE 2

Distribution of Nitrogen as percentage of Total Nitrogen among Physical Fractions of Human Faeces
(Tremolières *et al.*)

	Normal	Resection of small intestine	Insuffi- ciency	Recto- colitis	Cirr- hosis
Bacteria	17	28	12	12	23
Cellulose fractions	29	27	26	24	34
Amorphous heavy fractions	7	4	8	6	8
Water soluble	47	41	54	52	25

soluble fractions, heavy amorphous residues. Nearly 50 per cent of faecal nitrogen is in the water-soluble fraction, mainly in the form of by-products of amino-acid catabolism. In the diet used, bacteria are 15 to 20 per cent of the dry weight.

Thirty per cent of fats are water soluble and 38 per cent are absorbed by the very thin cellulose residues. Cellulose stored in the gut might be in large amounts, because 4 weeks after a cellulose-free diet there is still cellulose in the faeces. Faecal water has an osmolarity of about 150 mEq./L for cations (about 100 mEq. K and 50 mEq. Na) (J. Tremolières *et al.*⁴⁵). Normal and pathological characteristics of faeces are given in Tables 4 and 5.

TABLE 3

Distribution of Faecal Lipids as percentage of Total Lipids among Physical Fractions of Human Faeces
(Tremolières *et al.*)

	Normal	Atrophy of small intestine	Chronic Insuffi- ciency	Cirr- hosis
Bacteria	15	16	8	16
Cellulose	38	27	20	46
Amorphous heavy fractions	5	2	2	3
Water soluble	29	41	38	20
Free lipids	12	14	32	15

Effects of Fats on Digestion. Using a radiological method, Sarles²⁹ showed the different cholecystokinetic effects of different fats. Cocoa butter has a strong but short action. Eggs and hydrogenated copra have a strong and more prolonged effect. Butter, olive oil, beef fat and trielaidin have less cholecystokinetic effect. The cholesterol excreted in 24 hours in bile is related to the level of the caloric intake, the cholesterol excreted being proportional to the caloric intake. No relationship was observed with the amount and the nature of the fat ingested.

Sarles *et al.*³⁰ showed by dietary surveys on patients with biliary lithiasis that their general caloric intake is high, but that their fat intake is not higher than protein and carbohydrate implicate.

Clement¹⁰ studied *in vitro* hydrolysis of different fats by pancreatic lipase. The degree of hydrolysis in 90 minutes is proportional to the degree of unsaturated fatty acids except for short chain (lauric) fatty acids. Refined soya oil always has a higher degree of hydrolysis than crude soya oil. In accordance with the nature of fatty acids liberated during prolonged hydrolysis, Clement¹⁰ observed that saturated ones are liberated first and unsaturated later. For example, in the case of a

TABLE 4
Characteristics of Human Faeces
 (Tremolières et al.)

	Average weight for 24 hours (g.)							Percentage of dry weight					
	Fresh weight	Dry weight	Nitro- gen	Lipids	Cellu- lose and ashes	H ₂ O mEq	Na mEq.	K mEq.	Cellu- lose + ashes	Lipids	Proteids	Na mEq./ l. water	K mEq./ l. water
Normal (7 subj.)	133 ± 40	21 ± 5	1.1 0.1	3.5 ± 0.1	11.8	111	6.5 ± 3	11.3 ± 4	51	17	31	50	102
Large resection of small intestine. Severe pancreatic insufficiency. Cirrhosis (3 subj.).	340 ± 89	47.7 ± 10	2.77	20.5	9.9	292	22.1 ± 5.1	21.3 ± 3.3	20.1	43.3	37	75.6	
	307.5 ± 89	89.4	5.6	35.2	19.2	218	13.4	29.7	22.6	34.2	43.1	53.2	
	259 ± 157	34.8	1.85	5.25	19.5	213	2.26	36.4	57	15.3	27.9	9.6	

TABLE 5
Physical Fractions percentage in Dry Weight

	<i>Big residues</i>	<i>Thin cellulose</i>	<i>Amorphous and heavy fractions</i>	<i>Water soluble</i>	<i>Bacterias</i>	<i>Free lipids</i>
Normal (7 subj.) . . .	20.5 ± 4	28.5 ± 7	9 ± 2	26 ± 6	14 ± 3	2.1 ± 1
Large resection of small intestine	12.7	35	3	20.5	23.5	7.1
Severe pancreatic insufficiency	± 2.4	± 8.8	± 1.5	± 2.4	± 7	± 2.3
Cirrhosis (3 subj.) . . .	8.9	36.5	7	23.1	13.2	12.1
	33.6	11.1	8.8	29	14.2	2.6

fat with an iodine index of 71 for 12.5 per cent hydrolysis, the fatty acids liberated have an iodine index of 54 and remaining glycerides of 75.

When, in a customary human diet, 75 per cent of the fats are carefully controlled, the differences in the digestive utilization coefficient (DUC)

$$\text{DUC} = \frac{\text{total fat ingested} - \text{total faecal fats}}{\text{total fat ingested}}$$

over stable periods of 7 days, are not greater than random differences between one subject and another and even in the same subject after a period of time. In any case, differences are so insignificant that in humans they are of no nutritional interest. Figures of DUC in percentages are:

Butter	96 \pm 1.3
Hydrogenated copra	95.1 \pm 1
Refined arachid oil	96.7 \pm 1.1
Trielaidin	95.9 \pm 2
Sunflower-seed oil	92.1 \pm 2.5
Beef fat	95.5 \pm 2
Cocoa butter	92 \pm 3.2

Fifty to 75 per cent of these fats were included in the total lipids ingested, and for a period of 7 days.

Using the method of differential centrifugation mentioned above it was observed that from a very low fat diet to a normal fat diet the weight of the faeces and of its cellulose content is increased, in spite of the fact that the amount of cellulose in the diet is stable. It appears that the fats are adsorbed on thin cellulose residues whose storage in the caecum is reduced. Refined pea-nut and sunflower-seed oils have a slight laxative effect, increasing the water and sodium content of the faeces (Tremolières, *et al.*⁴⁶).

Food Additives

Manchon²³ showed that azoic colouring agents are reduced by the supernatant fraction of liver homogenates. Reduced triphosphopyridine nucleotide (TPNH) produced by reduction of glucose-6-phosphate (G-6-P) is the necessary cofactor. Further work showed that the relative activity of anaerobic to aerobic glycolysis is modified. Such facts as these indicated the necessity of extending the scope of toxicology from that of the rather prehistoric stage constituted by DL 50 and so-called chronic toxicity studies.

Nutritional Significance of Growth

A statistical analysis of growth records from 1942 to 1948 established the fact that average height and average weight are related to a great number of factors. After stratifying the sample as regards level of instruction, social group, number of children in the family, size of the city, heights varying by 3 to 4 cm. at 20 years of age and weights varying by 3 to 4 kg. may be observed. Therefore, comparing an average height or weight with any type of standard has no meaning, since the distribution of all these factors in the standards and in the population studied is usually unknown (J. Tremolières, *et al.*⁴³).

A longitudinal method of study was evolved. It is curious that the curves of weight distribution determined by all French measurements are nearly the same as Wetzels channels of development based on morphology. The level of development at a given age differs by 2 or 3 years from one district to another (J. Tremolières, *et al.*⁴⁴).

Recommended Dietary Allowances

Relating over a sufficient period of time the actual caloric consumption of a given population to standards, shows a deficit only if no correction for weight is made. If weight is taken into account, except for very short periods, a study of caloric consumption helps only to verify the equation giving the relation between caloric intake and weight. In this connection it was shown that, notwithstanding very different food habits throughout 24 areas in France, actual caloric consumption does not differ by more than 10 per cent of the standard. After a caloric reduction of 20 to 30 per cent as compared with the pre-war levels during the German occupation of big cities, which was accompanied by weight reduction, there was spontaneous compensatory over-consumption (J. Tremolières, *et al.*³⁹). One outstanding fact as regards caloric intake was that "sedentary workers" have an excess caloric intake of 20 to 30 per cent as compared to SDN standards, heavy workers being 10 per cent lower. It was concluded that the categories for workers were changing and that caloric expenditure outside working hours may have considerable influence.

The total protein consumption appears to be a very fixed proportion of the total caloric consumption (i.e. 12 per cent \pm 1 per cent of calories from protein) (J. Tremolières⁴¹). This was observed also in Morocco where it appears that the population would prefer to

reduce its total caloric intake rather than lower the percentage of calories derived from protein (J. Tremolières *et al.*⁴⁰). The total protein consumption of different groups in France is 20 to 30 per cent above the Société des Nations (SDN) standards of 1 g./kg., and even in Morocco, among certain poor groups in the population, the actual consumption of protein exceeds recent FAO protein standards. The discrepancy between the actual consumption of large populations probably for centuries and the opinion of a so-called group of international experts (i.e. the FAO group of protein requirements) calls forth a mark of interrogation. In view of the fact that it is physiologically wrong to consume only the minimum nitrogen intake necessary to maintain nitrogen balance and that the essentiality of amino acids (i.e. biological value) depends on the nutritional state, the Nutrition Section of the National Hygiene Institute was of the opinion that this Committee was wrong in extrapolating from very special experimental conditions to the ordinary life of men. As such international standards are used for economic projects and often, in fact, form the basis of calculations by "economic experts", the aforementioned critics were referred to a sentence of P. Valéry to which they might with advantage devote a little more thought "Une Société s'élève de la brutalité jusqu'à l'ordre. Comme la barbarie est l'ère du *fait*, il est donc nécessaire que l'ère de l'ordre soit l'empire des *fiction*s. . . . "Certains trouvent aujourd'hui que la conquête des choses par la science positive nous va conduisant ou reconduisant à une barbarie, quoique de forme laborieuse et rigoureuse; mais qui n'est que plus redoutable que les anciennes barbaries pour être plus exacte, plus universelle et infiniment plus puissante. Nous reviendrons à l'ère du *fait*—mais du *fait scientifique*". (P. Valéry. *Variétés—Préface aux Lettres Persanes*.)

Food groups appear to have increasing significance and usefulness. They facilitate the correlation of the 3 main aspects of food, i.e. nutritive, psycho-sensory and socio-economic. A classification based on these three criteria can serve as a basis for data in surveys concerned with nutrition, education, food, and community planning and control.

From actual consumption data based on surveys, the following standards were recommended:

TABLE 6

Actual Average Consumption by Food Groups in France (1948-50)
(g./day/person)

	<i>Group I</i> <i>Meat</i> <i>Sausages</i> <i>Fish</i> <i>Pulses</i>	<i>Group II</i> <i>Milk</i> <i>Cheese</i> (as milk)	<i>Group III</i> <i>Fats</i> <i>Butter</i>	<i>Group IV</i> <i>Cereals</i> <i>Bread</i>	<i>Group V</i> <i>Fruit</i> <i>Green</i> <i>vegetables</i>	<i>Group VI</i> <i>Potatoes</i> <i>Cooked</i> <i>vegetables</i>
Liberal worker	186	447	61	366	235	510
White collar worker	182	459	63	404	186	567
Manual worker	177	450	53	418	180	524
Heavy worker	186	463	50	435	180	500
Cities . . .	192	498	54	390	185	529
Rural . . .	297	470	49	509	45†	462
M.W.* . . .	243	564	75	487	198	704
M.W. C† . . .	195	529	61	425	170	544
M.W. CC . . .	172	488	53	395	151	510
M.W. CCC . . .	159	510	45	397	149	508
M.W. CCCC . . .	135	415	42	509	126	425

* Men—Women.

† Men—Women—one child.

‡ Winter.

From National Hygiene Surveys—*Bull. I.N.H.* vol. 7, No. 4.

Within each group basic foods are expressed in percentages of total for the group: meat and sausage (75 per cent), milk (66 per cent), butter (30 to 40 per cent), bread (80 per cent), potatoes (49 to 62 per cent).

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CHAPTER 32

NUTRITIONAL ANÆMIA

(With Special Reference to Tropical Regions)

by

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THE incidence of nutritional anæmia in the tropics is much greater than elsewhere and a common observation by practitioners there is that very many of their patients are, to a greater or lesser extent anæmic. The causes of the anæmia are not always easily determined and though much of it is of the microcytic, hypochromic type and responds to treatment with iron, some of it is relatively resistant to available remedies. In this chapter consideration will first be given to the prevalence of anæmias of nutritional origin, and this will be followed by discussions on iron deficiency anæmia, megaloblastic anæmia, anæmia associated with protein malnutrition and those associated with other possible ætiological factors.

The Frequency and Prevalence of Anæmia

The prevalence of anæmia and its importance to the public health are difficult to assess; hospital statistics give some information on these points but because the population served by particular hospitals is seldom known and because only a proportion of patients affected by any disease in the tropics seek hospital attention, the incidence of anæmia in a region can usually only be guessed. Nevertheless, it can generally be assumed that if a disease is commonly encountered in any hospital, then it is even more common in the local population than is suggested by the hospital figures. Because of the shifting nature of the population in many parts of the tropics, hospital figures in an area do not necessarily reflect the prevalence of disease in that area. For this reason, data collected in the relatively compact yet densely populated island of Mauritius is of special value for it is served by a unified network of small hospitals controlled by a single medical administration and the population of the island is relatively static. The value of this data is enhanced by the fact that malaria has recently been eradicated from the island, so that one of the variables in considering the ætiology of these anæmias has been

removed. The prevalence and relative importance of anæmia as a cause of morbidity on the island has been reported on by Woodruff (1958) and in brief can be approximately assessed by comparing numbers of patients treated for it in hospitals with the numbers of those treated for other diseases. Thus in 1948 only accidents, diseases of the skin and malaria, were responsible for more admissions than anæmia for which 1,592 patients were taken into hospital during the year from among a population of 450,000; but in 1953, by which time malaria had been eradicated from the island, the number of patients admitted for anæmia there had increased to 2,934 and was second only to accidents as a cause of admission to hospitals on the island. A feature of these anæmias is that many of them are severe and Woodruff (1955a) has reported that during the three months commencing July, 1955, there were referred to the Central Laboratory, Mauritius and its two branches, 145 patients with a hæmoglobin value of less than 3.5 g. per cent, a large number in relation to the population of Mauritius which is approximately 450,000.

In the Gambia, Woodruff and Schofield (1957) carried out a survey of hæmoglobin values and found that among males aged 17 to 45 years the mean value was 11.76 g. per 100 ml. blood, among non-pregnant women of similar age it was 10.12 g. and among pregnant women 9.09 g. Of 288 persons in the survey 31 or 10.7 per cent had a hæmoglobin value of less than 8 g. per 100 ml. blood.

From India there has now for upwards of 30 years been a steady stream of reports on the prevalence of anæmia, particularly in pregnancy. Muktha Sen (1955) working in West Bengal found anæmia to be the commonest cause of maternal mortality there, being responsible for 39 per cent of maternal deaths. Pandit (1948) has also drawn attention to the importance of anæmia as a cause of death in pregnant women. Anæmia has been found to be an important cause of prematurity and hence of stillbirths and of neonatal mortality. Das Gupta (1951) investigated 2,947 premature and immature births and found that severe secondary anæmias, mainly nutritional, were present in 73.2 per cent of the mothers concerned and "it can be inferred that these were responsible for causing the large number of premature and immature births". In Costa Rica 56 per cent of mothers having premature deliveries had hæmoglobins below 10.6 g. per 100 ml. blood (Cortes, 1955).

A survey of particular importance in that it included persons from all parts of India was that of Hynes, Ischaq and Morris (1945) who found that of 600 recruits to the Indian Army only 195 had a hæmo-

globin value of 51 per cent or more. Woodruff (1955b) has reported upon the high incidence of anæmia in India. In western Nigeria, Nicol (1952a) has reported that in one third of cases studied there, a clinical degree of anæmia is present.

There is general agreement that the majority of these anæmias are of the iron deficiency type, thus in Kenya, Foy *et al.* (1952) have reported that 80 per cent of the population are iron deficient. In Sierra Leonè, Gosden and Reid (1948) found that 34·9 per cent of adult males and 42·1 per cent of adult females exhibited hypochromia and microcytosis. Among Nigerian peasants, Nicol (1952b) reported that "the incidence of hepatic disease and anæmia, which is almost always hypochromic and microcytic in type, was high but the major nutritional diseases, beri-beri, pellagra and scurvy have not been encountered". In Kenya, Foy *et al.* (1952) estimated that iron deficiency affected 80 per cent of the indigenous population. In the non-tropics also iron deficiency has been reported to be the commonest cause of anæmia, thus Holly (1955) found that of 102 pregnant women with anæmia, it was the cause in 88. In Ohio, U.S.A., anæmia was found by Guest and Brown (1957) to be commonest in young children and to be iron deficient in type. Among Eskimos in Alaska 15 per cent of women in two villages had hæmoglobin levels below 10 g. per cent and in all, the red cells were microcytic and hypochromic (Scott *et al.*, 1955).

IRON DEFICIENCY ANÆMIA

Ætiology. The importance of knowledge concerning the causation of iron deficiency anæmia is increasing because of the interest now being taken in their elimination on a public health scale. The main basic causes of iron deficiency are (i) an inadequate dietary iron content, (ii) interference with absorption of iron from the intestine, (iii) excessive losses of iron from the body, (iv) disturbance of iron metabolism by infection or other mechanisms.

Dietary Iron. In assessing what is an inadequate dietary content of iron, it is necessary first to consider the normal requirements. Moore (1955) has reviewed the available information and concludes that the average person absorbs approximately 10 per cent of the dietary iron. To maintain positive iron balance, the amount contained in the food of adult males should, he considers, be not less than 12–15 mg. per day and that of pregnant women approximately 20 mg. per day. The daily requirement, averaged throughout the whole of the first 20 years of life amounts to approximately 10 mg. per day of which approximately 1 mg. per day will be absorbed. Iron

requirements are relatively high towards the end of the first year of life and during adolescence when growth rates are rapid. At the end of the first year the relatively large demand may favour inadequacy of dietary iron particularly among those who have been born prematurely with consequently restricted iron stores.

Bearing these iron requirements in mind, recent surveys indicate that the majority of inhabitants both of tropical and temperate regions have an adequate dietary iron content. Among tropical countries, an outstanding amount of data is available from India. Thus among south Indian plantation workers Ramalingaswami and Patwardhan (1949) found the average iron content of the diet to be 20 mg. per day. In Bombay State Radhakrishna Rao (1954) found the iron intake in 37 out of 185 persons to be 16.5 mg. per day and in the remainder of the 185 to be in excess of this. There is evidence, however, that in some persons in India a true dietary deficiency of iron may exist for Mitra (1953) found 6.5 per cent of 843 Indian families to have a dietary iron intake of less than 15 mg. per day. In North Carolina and in Tennessee, adequate amounts were respectively reported by Millam and Muench (1946) and by Youmans *et al.* (1943). In Nigeria, the diets of farmers, traders and fishermen were found to contain between 21 and 57 mg. iron per day (Nicol, 1952b). Further south in Africa the South African Bantu have been reported to consume a diet containing between 30 and 200 mg. iron per day (Walker and Arvidsson, 1953). In Venezuela the daily dietary intake for the population of the whole country is considered, on the basis of known food production, exports and imports for the country to approximate to 12.4 mg. (Bengoa and Coll, 1950.) A detailed study, however, carried out over 7 days, of the diets of 49 Venezuelan families revealed that they consumed an average of 19.4 mg. iron per person per day (Bengoa, 1950).

From these figures it seems that true dietary deficiency of iron is likely to occur in only a small minority of persons and that in almost all cases therefore, in which iron deficiency has developed it has resulted from other factors which have either caused excessive losses of iron or conditioned its absorption or utilization.

Interference with Absorption of Iron. Among factors which may interfere with the absorption of iron, interest has latterly centred around phytates, phosphates and calcium.

It was shown by McCance *et al.* (1943) that when phytate was added to bread and given with iron salts to normal persons, impairment of absorption, as judged by serum iron levels, occurred particularly of ferric salts. A high phytate content of the diet has

therefore been postulated as a factor inhibiting absorption of iron from the intestine and thus rendering inadequate an apparently adequate dietary iron content. A complicating factor is, however, that Sharpe *et al.* (1950) have found that diets rich in phytate are usually bulky and that there is an inverse relationship between the total solid content of diets and the percentage absorption of iron from them.

Phosphates also combine with iron to form insoluble salts and there is evidence that iron absorption is increased by lowering the phosphate content of a diet (Hegsted *et al.*, 1952). It has been suggested that iron deficiency anæmia in some parts of India may be the result of the high phytate and phosphate content of local diets (Foy and Kondi, 1956c).

A high calcium content of the diet has been inferred to have a deleterious effect upon iron absorption for Greig (1952) produced iron deficiency anæmia in mice by feeding them a diet rich in calcium and showed that this anæmia could be prevented by simultaneous administration of ferric citrate.

This subject is, however, complex for a high calcium content of the diet might be expected to compete with iron for phosphate and thus release iron for absorption (Brock and Diamond, 1934; Brock, 1937). Much will clearly depend on the relative amounts of calcium, iron and phosphate in the diet; if for example there is much calcium and little phosphate the calcium might impair iron absorption but in a diet containing an excess of phosphate a high calcium content could presumably assist iron absorption.

Excessive Loss of Iron. Excessive loss of iron from the body may result in iron deficiency even in those who are otherwise taking a satisfactory amount of iron in their diet. Such factors do not strictly come within the nutritional field although they may effect nutritional requirements; they have been reviewed by Woodruff (1960). In brief the main tropical factors thought likely to be responsible for excessive losses are hookworm infections and excessive sweating in the hot and humid parts of the tropics; of these two factors hookworm infections appear to be much the more important.

Bacterial and Other Non-helminthic Infections. These like excessive losses of iron do not strictly come within the nutritional field but may affect nutritional requirements; they have been reviewed by Woodruff (1960). Malaria in infancy, early childhood and in non-immune adults may give rise to anæmia but does not normally cause iron deficiency; its importance as a cause of chronic anæmia in semi-immune populations is more doubtful.

Bacterial infections may be among the important causes of anæmia generally, and, particularly among children they have been considered so by Diamond (1950). Anæmias produced by bacterial infections may be both microcytic and hypochromic though more commonly they are normocytic and normochromic (Cartwright and Wintrobe, 1955).

Increased Requirements of Iron

The latter part of the first year of life, adolescence and pregnancy are known to be the periods at which iron deficiency anæmia most commonly occurs and these periods are those in which the demand for iron is maximal. Important studies of iron balance have been carried out by Moore (1955). Most new-born infants begin life with 300 to 500 mg. iron stored in their body and 2·5 to 4·5 g. iron are laid down in the tissues during the following 20 years, i.e. an average of 0·35 to 0·6 mg. per day during this period. During the same period iron losses approximate to 0·6 mg. per day and as approximately 10 per cent of dietary iron is absorbed the mean daily dietary iron requirement during the first 20 years of life is not less than 10 mg. The iron requirement of full-term babies is met by that contained in normal mothers' milk and is approximately 0·15 mg. per kilo per day (Josephs, 1953). The requirement increases from this amount and during adolescence approximates to or exceeds that of adult life. Average excretion by adult males is 1 mg. per day and as most diets contain 12 to 15 mg. iron per day from which 10 per cent is absorbed, 1·2 to 1·5 mg. daily appears to be sufficient for the requirements of most adult males. Women, however, require an additional 0·5 to 1 mg. per day to balance menstrual losses. During pregnancy, the demand is slightly greater still, averaging between 1 and 2 mg. per day throughout pregnancy, i.e. rather more is needed than is saved due to cessation of menstruation. The demand for iron during pregnancy is necessitated by the 300 to 500 mg. contained in the foetus and by approximately 325 mg. required for growth of the uterus and placenta and for normal blood loss. A similar demand for iron continues throughout the period of lactation during which approximately 1 mg. per day is lost in milk. The importance as a cause of anæmia, of repeated pregnancy before the age of 19 years has been emphasized by Foy and Kondi (1957). Pregnancy at this time imposes a particular strain on reserves in that normal bodily growth has not then ceased and the volume of blood is still expanding.

Prophylaxis and Treatment

It is during periods of especially rapid growth of tissues, such as late infancy, adolescence and pregnancy, that prophylaxis is most important and it is particularly important at these times in communities in which there is a high rate of infection with hookworms.

Infants. The provision of supplementary feeding to infants aged 6 months and over will usually prevent the development of anæmia and supplements of particular value are soups prepared from meat and green vegetables, vegetable puree and eggs. For infants with anæmia, ferrous sulphate or one of the scale preparations (iron and ammonium citrate or iron and quinine citrate) may be given, ferrous sulphate in doses of 15 mg. ($\frac{1}{4}$ grain) thrice daily or one of the scale preparations in doses of 100 mg. ($1\frac{1}{2}$ grains) also thrice daily. These doses may be doubled if the hæmoglobin is below 11.5 g. per cent.

Adolescents and Pregnant Women. Ferrous sulphate is not only the most effective iron compound for therapy and prophylaxis but it is also the cheapest. It may be given in doses of 60–200 mg. (1 to 3 grains) once daily for prophylaxis or thrice daily for treatment of established anæmia. Ferrous gluconate is an alternative preparation and for treatment of anæmia, 300 to 600 mg. of it may be given thrice daily and proportionately smaller amounts for prophylaxis. The so-called physiological anæmia of pregnancy which has been attributed to a rise in blood volume at that time, has been shown by Davis and Jennison (1954) and Fisher and Biggs (1955) to be prevented by adequate iron administration. It must therefore be regarded as resulting from a dietary iron content inadequate for the demands of pregnancy.

For either prophylaxis or treatment a diet rich in ascorbic acid is an advantage in view of its value in assisting the absorption of iron. In Mauritius, iron deficiency anæmia and hookworm infection are both common and Stott (1959) found that the former could be prevented by a supplement of as little as 6 mg. elemental iron a day.

The importance of an adequate amount of protein in the diet of those being treated for anæmia has been underlined by the work of Foy and Kondi (1957) who have shown that treatment of such patients with iron alone may result in the hæmoglobin rising to approximately 11 to 12 g. per cent at which level further iron therapy produces no additional response until a supplement of protein is added to the diet. Gaisford (1960) has emphasized that good therapeutic results in iron deficiency anæmia are unlikely to occur in the

presence of an infection which should therefore be treated first. As a corollary to this, failure of response in an undoubted case of iron deficiency should lead to a search for an infection.

Intravenously administered iron is seldom required and for general purposes iron should not be given intramuscularly unless there are special indications for so doing in view of the presumed carcinogenic effects of the iron-dextran preparations used for this purpose (*Brit. med. J.*, 1960).

Nutritional Megaloblastic Anæmia

Although the incidence of megaloblastic anæmia of non-Addisonian type is difficult to determine, many reports concerning it have emanated from India, the Far East, Africa, the Caribbean and Central America. Points of special interest concerning megaloblastic anæmia are firstly that treatment with parenterally administered penicillin has been found in certain cases to induce a therapeutic response, presumably by modifying intestinal bacterial flora and secondly that recent work has shown that megaloblastic change is not uncommon in certain hæmolytic anæmias, presumably because the increased blood regeneration occurring in these anæmias leads to an increased demand for specific hæmopoietic substance.

Clinical and Pathological Features

Many patients with non-Addisonian megaloblastic anæmia present with a strikingly low hæmoglobin level and with corresponding weakness and dyspnœa. Mild hæmolytic jaundice is not uncommon and occasionally slight fever or œdema have been reported. The tongue is rarely sore and involvement of the central nervous system is also uncommon (Foy and Kondi, 1956b).

The hæmoglobin values in these cases are commonly between 2 and 5 g. per 100 ml. blood, the red blood cell count may be considerably below 1,000,000 cells per cu. mm. and the mean corpuscular volume (MCV) is usually higher than the upper limit of the normal range which is 95 cu. microns. Megaloblastic anæmias are, however, not always macrocytic as judged by the MCV and macrocytic anæmias are not always megaloblastic. This dissociation between the marrow and the peripheral blood picture has been reported by Foy *et al.* (1950a) and by Woodruff (1951). In some cases no megaloblasts are present in the marrow but there may be giant stab-cells. In these cases the therapeutic response is similar to that occurring in those with megaloblasts in the marrow (Foy *et al.*, 1950b). Intra-vascular hæmolysis is usually increased and is evidenced by a

positive Schumm's test (Foy and Kondi, 1956b). Reticulocytes are usually diminished in number. From the gastric juice, acid is absent a little more frequently than it is from a sample of the healthy population. The serum vitamin B₁₂ levels which are normally between 300 and 500 micro-micrograms per ml. are commonly reduced to 50 to 100 micro-micrograms per ml. but in a few cases the value may be 900 to 1,500 micro-micrograms per ml. and in these there is a therapeutic response to administration of folic acid but not to vitamin B₁₂ (Foy and Kondi, 1956b).

Megaloblastosis in Hæmolytic Anæmia. Megaloblastosis has been known for some years to occur at times, in association with hæmolytic anæmia. Thus Davidson (1952) and Drury and Geoghegan (1952) have reported it in association with congenital spherocytic anæmia (acholuric jaundice) and Kohler *et al.* (1960) have recently described a further case. Similar development of megaloblastosis has been recorded during pregnancy in a patient suffering from thalassemia (Goldberg and Schwartz, 1954) and in a young Scillian with thalassemia by Crosby and Sacks (1949). Particular interest has been aroused by the recent discovery of megaloblastosis in association with other hæmoglobinopathies in which there is increased hæmolysis of red blood cells. Thus it has been described in sickle-cell anæmia and sickle-cell hæmoglobin C disease by Jonson *et al.* (1959), and in sickle-cell anæmia by Hilkovitz (1960) and by MacIver and Went (1960). It seems probable that the common denominator to the megaloblastosis in these hæmolytic states is the increased demand imposed upon the patient's supplies of hæmopoietic factor by a persistently active marrow regenerating erythrocytes to replace those hæmolysed.

Treatment. Rational treatment in these cases can only be carried out after thorough investigation and the opportunity should, whenever possible, be taken to learn something of the cause of the anæmia from the results of treatment. Small amounts of hæmatinics are often used for this purpose and the response to graded quantities studied. For routine treatment, however, folic acid brings forth a more constant response than vitamin B₁₂ and if the only aim is to bring about a rapid hæmatological improvement 50 mg. folic acid may be injected or administered orally on two successive days and followed by 20–30 mg. orally till the blood picture has returned to normal when the dose may be gradually reduced and then discontinued. Alternatively vitamin B₁₂ may be injected subcutaneously or intramuscularly in an initial dose of 50–1,000 microgrammes followed by 50 microgrammes twice weekly till the hæmoglobin is

normal when the dose may also be progressively reduced and discontinued. Orally administered vitamin B₁₂ has been found to be effective in doses of 40–80 microgrammes in some cases (Foy and Kondi, 1956b).

A response may be obtained to penicillin administered orally in daily doses of 200,000 units, or intramuscularly in doses of 400,000 units daily (Foy and Kondi, 1956b). Supportive therapy with iron and supplements of protein may be necessary for a full hæmatological response.

Ætiology

The responses of these anæmias to treatment have provided many indications of their causes and these have been studied in detail by Foy *et al.* (1950a, 1950b, 1954 and 1956b) and by others.

In some cases a satisfactory therapeutic response to treatment with vitamin B₁₂ is obtained and in these the serum vitamin B₁₂ levels are below the normal range (*vide supra*). Most patients who fail to respond to vitamin B₁₂ will respond to treatment with folic acid; in these the serum vitamin B₁₂ level is high, often reaching 900 to 1,500 micro-micrograms per ml. (Foy and Kondi, 1956b) and their ability to absorb vitamin B₁₂ as estimated by studies in which it has been radioactively labelled, is normal. It is now generally considered that the cases described 25 to 30 years ago by Wills (1931, 1932, 1933) fall into this class for they failed to respond to refined liver extract but responded to treatment with marmite which is known to contain significant amounts of folic acid.

Penicillin, administered either intramuscularly or orally, has been found to induce reticulocyte crises and hæmatological improvement in some cases of megaloblastic anæmia (Foy and Kondi, 1954). Those patients who fail to respond to penicillin, do so to folic acid. There are, however, some cases in which there is no response to penicillin but there is a response to intramuscularly administered, but not orally administered, vitamin B₁₂. Penicillin seems to benefit only those who respond to orally administered vitamin B₁₂. It is clear that it does not have a direct hæmopoietic effect but its action is presumably mediated by the synthesis, absorption or availability of vitamin B₁₂ in the intestine. Such an action might well result from effects on the bacterial flora of the gut, some of which may absorb vitamin B₁₂ from the intestinal contents and some of which may synthesize it. Penicillin could destroy bacteria which compete for vitamin B₁₂ or favour the growth of bacteria which synthesize or lyse bacteria containing it and thus liberate it from them. It is

probable that of these possible mechanisms the most usually operative is competition for vitamin B₁₂ by bacteria in the intestinal canal together with consumption of a diet which is inimical to the synthesis of the vitamin or which encourages the multiplication of competitors for it. In this connection it has been pointed out (Foy and Kondi, 1956b) that the majority of patients with non-pernicious megaloblastic anæmia are from areas in which the diet is low in first-class protein and in which bulky carbohydrate is its main constituent. This view is supported by the observation that those patients who respond to penicillin and vitamin B₁₂ always have a low serum vitamin B₁₂ value, that absorption tests using radioactively labelled vitamin B₁₂ indicate that intrinsic hæmopoietic factor is excreted by these patients and that absorption of the vitamin from the intestine is adequate. The fæces of most of these patients contain large amounts of vitamin B₁₂, of the order of 30 to 80 microgrammes per day (Foy and Kondi, 1956b) yet the amount of the vitamin required to prevent the development of megaloblastic anæmia is only approximately 1 microgram per day. It thus seems probable that in these cases the bacteria in the intestinal canal compete successfully for vitamin B₁₂ which is then lost to the body in the bacteria contained in the fæces.

Concerning the detailed cause of these megaloblastic anæmias, some speculation is necessary for in almost all studies of them investigators have been presented with the end result of a process which may well have been going on for a considerable period and there are formidable difficulties in the way of studying over a long period, the diets of those who develop such anæmias. It appears probable that some diets, low in animal protein and rich in carbohydrate, may contain insufficient vitamin B₁₂ to prevent the development of megaloblastic anæmia. Such vitamin B₁₂ deficiency has been observed in patients with megaloblastic anæmia in Singapore (Wells, 1958) and in vegans who exclude from their diet all foods of animal origin including not only meat but milk, cheese and eggs (Wokes *et al.*, 1955; Sinclair, 1955). Alternatively, disturbances of the bacterial flora in the gut and competition by bacteria for vitamin B₁₂ may result in deficiency of the vitamin (*vide supra*). In such cases serum vitamin B₁₂ levels will be low and the patient will respond to oral administration of the vitamin. Megaloblastic anæmias in which serum vitamin B₁₂ levels are normal, however, are not uncommon and respond to treatment with folic acid. It is conceivable that in these cases the diet has been deficient of folic acid which is contained in fresh green vegetables, liver, kidney,

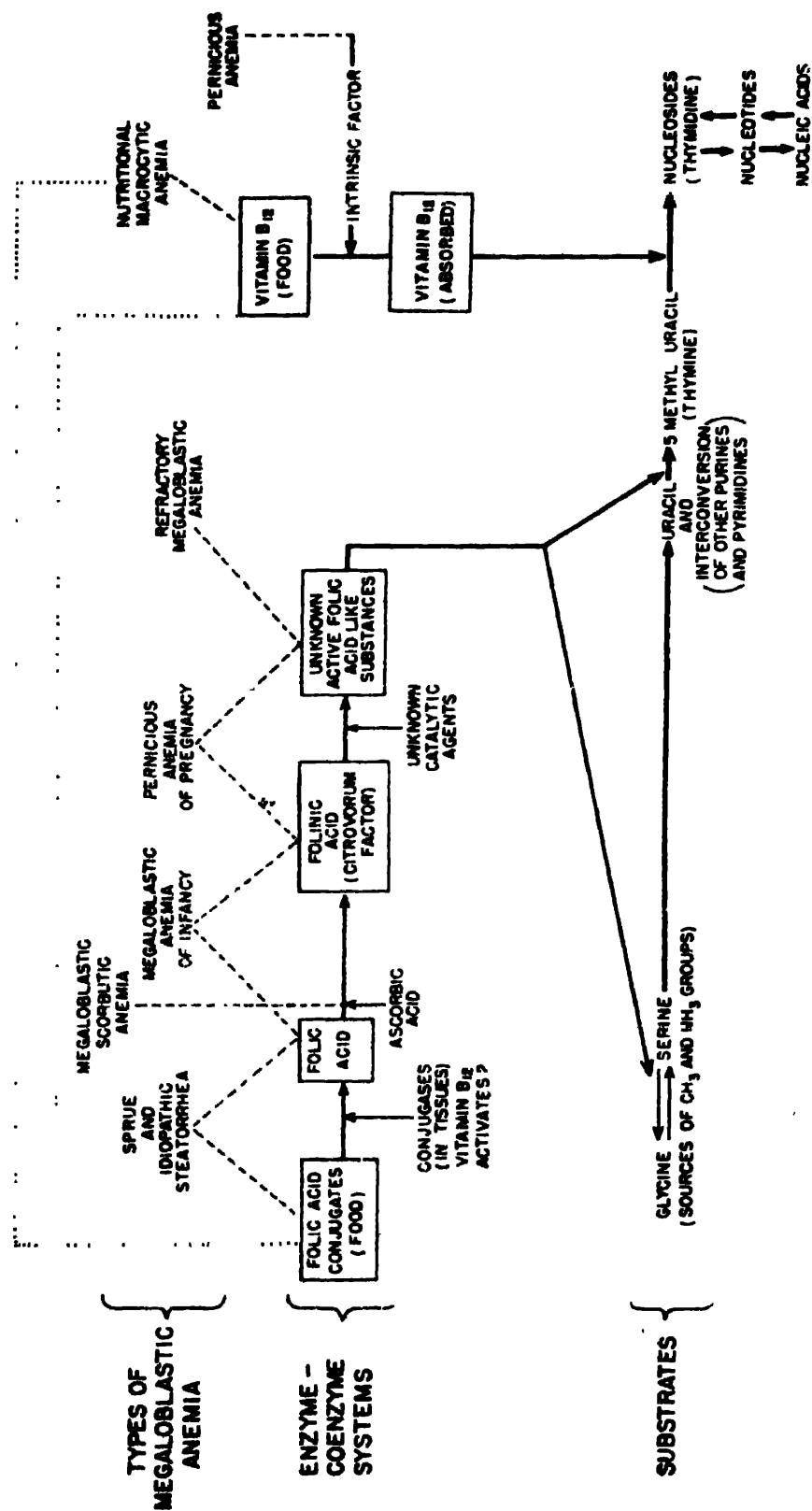


Fig. 1. Scheme showing possible ways in which megaloblastic anaemia may result from interference at different stages in the synthesis of nucleic acid of the erythromocyte precursors (Mueller & Will, 1955).

meat and to a lesser extent cereals and dairy products. Many of those who develop this type of anæmia have, however, lived on a diet containing an adequacy of green leafy vegetables and this, together with the observation that doses of folic acid in excess of those expected to be required for physiological purposes, have led to the suspicion that in such cases the folic acid is acting pharmacologically or by a kind of mass action rather than physiologically as a vitamin which is being replaced after having been deficient in the patient. Schofield (1957) has described cases in which very large doses of folic acid were needed in patients with megaloblastic anæmia in pregnancy.

Folic acid and vitamin B₁₂ appear to be required in different stages in the synthesis of nucleic acid and if absent, or prevented from acting at the required stage will result in megaloblastosis. Vilter *et al.* (1950) have devised a scheme, based on an earlier scheme of Mueller and Will (1955) in which the possible effects of these vitamins at different stages in the synthesis of nucleic acid are shown (Fig. 1).

ANÆMIA AND PROTEIN MALNUTRITION

Not all anæmias respond to treatment with iron, vitamin B₁₂ or folic acid and, particularly in the tropics, refractory cases of this kind are numerous. They are encountered especially during pregnancy, infancy and childhood and during the latter two phases of life are usually associated with one or more features of the kwashiorkor syndrome. Moreover, Trowell (1947) stated that when cases of macrocytic anæmia and dimorphic anæmia in African men and non-pregnant women are investigated in Uganda, a large number are found to show one or more of the features of the kwashiorkor syndrome.

On the basis of an extensive tour of Africa during which many centres were visited in which patients with protein malnutrition were studied and also after reviewing the literature Brock and Autret (1952) concluded that the anæmia in kwashiorkor is usually mild and either normocytic or slightly macrocytic except when parasitic infections are present when the anæmia may be very severe. Woodruff (1951 and 1955c) has also described such anæmia in association with protein malnutrition.

The classical experimental work of Whipple and Madden (1949) and Yule *et al.* (1951) has provided a basis for the understanding of the mechanisms whereby protein malnutrition may lead to anæmia. From these experiments it appears that hæmoglobin may be synthesized from plasma proteins and that among the plasma proteins, the

most labile is the globulin fibrinogen which is wholly dependent for production upon normal liver epithelium. The importance of the liver they consider, corresponds to its great size and strategical situation as the master organ in protein metabolism. The majority of protein synthesis within the body goes on in the liver in which evidence indicates albumen and probably some of the globulins are synthesized. They consider it possible that the fundamental protein for body exchange is albumen and that globulins are slight modifications of the albumen effected by the liver cell, reticulo-endothelial cell, muscle or other body cells. In experiments with dogs they showed that plasma could supply proteins out of which the depleted animal could manufacture new hæmoglobin and that 100 g. casein digest enabled 25–40 g. of new hæmoglobin and plasma protein to be produced. From their work they developed the concept of a large protein pool including the circulating plasma proteins and mobile cell proteins, contributions to which derived largely from the liver and from which may be derived hæmoglobin, new plasma protein or cell protein. Infection and intoxication may slow the response and utilization of proteins. It appears from the work of Nizet and Robschey-Robbins (1950) that the red blood cell at the reticulocyte stage is able to incorporate plasma proteins into itself or synthesize plasma proteins from amino-acids and that if the plasma proteins are abnormal or deficient, delay in reticulocyte ripening occurs. Application of these principles in clinical practice was illustrated by Holmes (1945) who reported the occurrence of œdema and effusions into serous cavities in patients recovering from anæmia. The œdema appeared to be the result of lowering of the plasma osmotic pressure consequent upon diversion of protein from the plasma to hæmoglobin synthesis.

Clinical Features. The anæmia in patients with protein malnutrition is as already stated usually of mild or moderate degree and is usually associated with other clinical manifestations of the protein malnutrition and also with clinical manifestations of other inter-current disease such as iron deficiency or parasitic infection. When, however, the condition is studied in its pure form it is found to be normocytic or slightly macrocytic. The mean corpuscular volume (MCV) is commonly at the upper limit of the normal range or slightly greater than this value, *i.e.* 95 cu. microns or more. Even when the MCV is normal, however, the mean corpuscular diameter (MCD) is often increased above the upper limit of the normal range which is 7.7 microns and as in these cases the MCV is usually but little raised the mean corpuscular average thickness (MCAT)

is correspondingly reduced. Woodruff (1955c) studied these indices in detail in protein malnutrition in childhood, in pregnant women and in older children, adult males and non-pregnant females. These findings are of special interest in view of the work of Larsen (1948) who showed that erythrocytes in acute and chronic hepatitis are abnormally broad and thin, the MCV in such patients usually is normal and, the standard deviation of the MCD is increased. In patients with anæmia and protein malnutrition there is almost invariably considerable liver damage so that the changes in red cell shape both in anæmia with protein malnutrition and in Larsen's cases are probably of similar causation. The broadening and thinning of erythrocytes, described by Trowell (1949) under the term dimorphic anæmia, may well be a result of this mechanism for such thinning gives to them the appearance of hypochromia while the broadening makes them appear macrocytic. This dimorphism has been attributed by Lehmann (1949) to the presence of reticulocytes which are larger than mature erythrocytes and which therefore raise the mean cell diameter of blood in which they are numerous. The reticulocytes, Lehmann considered to be the result of active blood regeneration consequent upon the presence of hookworms and other parasites. This is no doubt a factor operating in many cases but other factors are also important. Thus both Charles (quoted by Brock and Autret, 1952) and Woodruff (1955) have described cases in which a broad or biphasic Price-Jones curve has been obtained and in which the MCD of the erythrocytes was increased and could not be explained by reticulocytosis.

The marrow in these cases is commonly of the macronormoblastic type though in some 9 per cent of cases megaloblastosis may be present (Walt *et al.*, 1957).

The basic blood picture in protein malnutrition is of a normocytic anæmia with slightly broad and slightly thin cells and a macronormoblastic marrow but the characteristics of the erythrocytes are often obscured by superadded iron deficiency, by malaria or, less frequently, by megaloblastic change. It is to be expected that a patient suffering from protein malnutrition will also not uncommonly suffer from deficiency of other nutrients for the diet poor in protein is usually a very poor diet and those who take it are usually living in surroundings in which they are exposed to many infections.

The liver and spleen in these cases exhibit the clinical and pathological changes to be expected in protein malnutrition and in a series of cases reported by Woodruff (1955) ascites was a prominent feature and was associated with severe liver damage and low plasma

albumen values. Haemolytic features are common and in consequence the serum bilirubin may be increased and a positive Schumm's test be present. Hypertrophy of the reticulo-endothelial tissue in liver and spleen probably plays a part in this haemolysis as has been suggested by Fairley *et al.* (1938).

Treatment. Intercurrent infections such as malaria and helminthic disease should if possible be cleared up but in spite of so doing many patients remain anæmic. The response in these cases to a diet rich in protein is a slow improvement in the hæmoglobin (Woodruff, 1955c, Walt, 1959). In patients with kwashiokor, therapy with protein may often result in resolution of the symptoms of kwashiokor *per se* before any marked improvement has occurred in the anæmia. Following severe malnutrition, repletion of body proteins is a slow process. Considerable and long-sustained protein retention by malnourished persons fed a high protein diet has been reported from East Africa by Holmes *et al.* (1954) and from West Africa by Phillips and Ladell (1959). The latter showed that some persons fed more than 100 g. protein daily for 10 days continued to retain nitrogen and even lost weight. Such results are understandable in the light of the work done by Elman *et al.* (1942) who from experiments on dogs found a deficiency of 1 g. plasma protein to be equivalent to one of approximately 30 g. of body protein and that only after the total body protein deficit has been replaced does permanent elevation of plasma protein occur. A considerable time taken to replete body protein may account for some of the delay in improvement in hæmoglobin levels in these cases and persistence of hæmolysis due to a hypertrophied reticulo-endothelial system and to liver and spleen damage may account for further delay. The profound metabolic disturbance which may result from protein malnutrition has been referred to by Walt (1959) by Woodruff (1955c) and in connection with upset enzyme systems in many of Waterlow's writings (Waterlow, 1958 and Waterlow, 1959). The situation has been admirably summed up by Trowell (1960) who in discussing various abnormalities probably acquired during periods of malnutrition in infancy stated "at first they are quickly reversible by improved feeding, but after a time and in adult life many months or years may be required to change back to the 'normal'".

OTHER POSSIBLE NUTRITIONAL ANÆMIAS

Experimental work in animals has shown that in tryptophane deficiency a hypochromic anæmia may occur (Albanese *et al.* 1953).

Supplements of tryptophane will prevent this anæmia even when the diet of the animals is barely adequate to maintain life.

There is experimental evidence that pyridoxine deficiency causes hypochromic anæmia in animals (Dinning and Gay, 1956). In man the evidence is more slender but Snyderman *et al.* (1950) and Foy and Kondi (1958) have reported cases in which hypochromic anæmia responded to pyridoxine after failing to respond to iron.

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CHAPTER 33

HUMAN NUTRITION AND THE UNITED NATIONS AGENCIES

**PREPARED BY THE NUTRITION UNIT OF WHO, AND THE
NUTRITION DIVISION OF FAO.**

MAN'S food is one of the dominating environmental influences affecting his health and well-being during his entire life span. The nutrition of peoples throughout the world is therefore one of the greatest international problems of the present day and has received a great deal of attention from the international agencies, particularly FAO, WHO and UNICEF.

The technical aspects of programmes to improve the nutritional status of the different peoples are the essential responsibility of FAO and WHO. In WHO the emphasis is on nutrition in relation to the maintenance of health and the prevention of disease. In FAO the emphasis is on nutrition in relation to the production, distribution and consumption of food.

Food Consumption and Planning

Information on existing consumption levels and on nutritional status is needed before attempts are made for improving nutrition in any country. Assistance to Governments in establishing national food balance sheets, in conducting food consumption surveys and in formulating national food policies and plans is one of the important activities of FAO. FAO is preparing a draft programme of work on food consumption surveys, to be adapted to local conditions in developing regions.

An FAO publication on methodology of dietary surveys was issued in 1949,¹ and a new one dealing specifically with problems encountered in less developed countries will be issued in the near future.

Assessment of nutritional status is one of WHO's responsibilities. It is always desirable to conduct surveys of both diet and nutritional status simultaneously in the same population groups. FAO and WHO have been co-operating in joint surveys of this type in various countries.

Nutritional Requirements

Among the physiological problems of greatest importance to international agencies concerned with nutrition is that of human requirements for calories and nutrients. Knowledge of requirements is needed in FAO for the periodic appraisal of the food situation (on a global, regional or national basis) and for the planning of food production, while WHO is interested from the public health point of view.

Two meetings of experts on calorie requirements were organized by FAO in 1949² and in 1956,³ respectively. The recommendations of these meetings have been widely used not only by FAO but also by member countries and by nutrition workers all over the world.

The problem of protein requirements was discussed at various international conferences and meetings; a small FAO expert committee late in 1955 had the difficult task of reviewing the available knowledge and drawing up recommendations. Its report published in 1957,⁴ is of a provisional nature and will need revision in the light of further research in this field.

There is incomplete information on the problem of calcium requirement to enable recommendations for consumption levels to be made with any certainty. An Expert Committee on calcium requirements is being planned for 1961.

Protein Malnutrition

Kwashiorkor, essentially a disease of early childhood, is responsible for much morbidity and mortality in populations in the less-developed countries throughout the world. It is only in recent years, however, that its importance has been fully recognized. Just over ten years ago, FAO and WHO decided that the greatest emphasis in its nutrition programme should be directed to this problem. The first step was a survey carried out in Central Africa.⁵ Similar surveys in countries in Latin America and Asia^{6, 7, 8} together with surveys conducted by national administrations have shown that this disease is universal in the less-developed countries, though there are minor regional differences.

WHO and FAO have stimulated further interest in this problem in various other ways. In 1952 the Joint Expert Committee on Nutrition devoted its session to kwashiorkor. This took place in West Africa after the second Inter-African Conference on Nutrition sponsored by the Commission for Technical Co-operation in Africa south of the Sahara (CCTA) which devoted also considerable time to

the clinical, laboratory and preventive aspects of kwashiorkor. Since the members of the Joint Expert Committee who came from countries outside Africa also attended the CCTA meeting, there was ample opportunity for the exchange of ideas between workers from a wide geographical area.

In 1953 WHO and FAO with financial assistance from the Josiah Macy, Jr. Foundation, sponsored a meeting in Jamaica of workers from different parts of the world engaged in research into the various aspects of kwashiorkor.⁹ This meeting greatly influenced programmes of research which have since developed.

One way to prevent protein malnutrition is to find a cheap source of good protein in the areas where there is little or none. Since animal protein is expensive almost everywhere, attention has to be given to protein from vegetable sources. Between 1952 and 1954 WHO gave grants to three research centres in East Africa, Central America and South India to help them in their work on the suitability of various vegetable proteins for feeding of infants and young children. Exchange visits between these centres, arranged by WHO, served in co-ordinating their research.

In 1955 a second WHO/FAO Conference on Protein Malnutrition was held in Princeton,¹⁰ again with assistance from the Josiah Macy, Jr. Foundation. This meeting considered protein requirements and the means of meeting them in the younger age groups in populations that do not have access to the common protein-rich foods.

In the programme that has since developed, with assistance from FAO, WHO and UNICEF, much emphasis has been placed on the utilization of the by-products of industrial processing of natural foods such as peanuts, soya beans and oil seeds. Since these have not been widely used in human nutrition, and never before as a source of protein for young children, extensive preliminary trials were required in order to establish their safety, digestibility and nutritional value.

Very specialized knowledge is needed in this work and programme, and in 1955 WHO formed an Advisory Group from its panel of nutrition experts to assist WHO. All members were medical men, but more recently the Group has been re-organized to advise FAO and UNICEF as well as WHO. The membership now includes biochemists and others competent in different aspects of the whole programme, which is concerned with food processing, animal experiment, human physiology, treatment of disease and public health preventive procedures. Between 1956 and 1958 a Rockefeller Foundation grant of \$500,000 provided a great stimulus to this research. From this

money, grants are given by a committee of the National Research Council of the U.S.A. (with advice from WHO and FAO) to competent workers in this field. As a result, several products have emerged which have been sufficiently tested and can now be used safely for feeding young children.

Peanut flour obtained from solvent extracted peanuts, is now ready for large-scale production and marketing in Nigeria, Senegal and India. Mixtures of peanut flour with Bengal gram or Sesame flour are under trial in India, while mixtures with skim milk are being given to malnourished and very young children in Nigeria. A mixture of whole peanuts with skim milk and cottonseed oil is being used in large-scale feeding programmes in Uganda.

A soya bean and sesame flour mixture is now being produced in Indonesia under the name of Saridele, and its suitability for young children is being investigated.

Cotton seed flour mixed with corn (maize) meal, sorghum meal and torula yeast developed by the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala, is now on the open market under the name of INCAPARINA.

Extensive work on fish flour has also been carried out. In many countries where protein malnutrition is common, there are great possibilities for expanding the fishing industry; and the preparation of edible fish flour provides a protein-rich food which can be easily utilized for child feeding. Properly processed fish flour retains the biological value of the original material, keeps well and can, without much difficulty, be incorporated into local foods and dishes.¹¹

Acceptability tests with fish flour have been carried out with FAO assistance in many countries, with overall satisfactory results.

A plant for fish flour production has been set up in Chile, with the financial support of UNICEF; in Morocco, FAO has been advising private industry on the development of an edible fish flour. In the same country, a campaign to increase the consumption of fish and fish products, including fish flour, is being launched this year with FAO and UNICEF assistance.

A matter which is now receiving attention, and which perhaps should have been more prominent in the programmes in the past, is the consumption of natural locally grown protein-rich foodstuffs by young children. Of particular importance in this regard are the pulses. Work in Calcutta has demonstrated that a safe mixture for children 1-5 years of age can be prepared. Work is now going on with a similar food for infants of 1-2 years of age.

Endemic Goitre

Another widespread deficiency disease, endemic goitre, was included in WHO's activities relatively early in the Organization's history. The total number of goitrous people in the world is estimated at close on 200 millions. During the past 40 years, however, considerable progress has been made in the prevention of endemic goitre in such countries as the U.S.A. and Switzerland, mainly through the use of iodized salt.

At the end of 1952, following a recommendation of the Third World Health Assembly, a WHO study group in London recommended a standardized technique to be used in surveys, indicating the methods for enriching salt with either iodide or iodate, and mentioning the areas for further research.¹² Following this, the Third FAO/WHO Conference on Nutrition Problems in Latin America held in Caracas in 1953, made more detailed recommendations on survey techniques, levels and methods of iodization of salt, particularly under tropical conditions and on problems of further research.¹³

WHO has before, and since these meetings, sent consultants to most of the countries in Latin America, and to countries in Europe, Africa and the Eastern Mediterranean and South East Asia.

Since the iodization of the crude salt used in most developing countries presents special problems regarding mixing, stability, etc., the Chilean Iodine Educational Bureau in London, at the initiative of WHO, studied these problems and evolved a simple technique which has proved successful on a small scale, and is easily adaptable to large-scale operation at low cost. The question of stability in tropical conditions was solved by replacing iodides by iodates, which proved more stable and of equally low toxicity. Well-controlled field experiments done by INCAP in Central America have shown the effectiveness and harmlessness of iodates.¹⁴

WHO's interest in the goitre problem is reflected in the publication of two issues of the WHO Bulletin exclusively devoted to the subject^{12, 15} in 1953 and 1958. A monograph on the same subject has now been published and contains contributions from prominent workers in this field.¹⁶

The outcome of all these efforts has been that a method is now available for preventing endemic goitre wherever it occurs. Research is needed, however, as has been advocated by the Joint FAO/WHO Committee on Nutrition in 1954,¹⁷ to evaluate the effectiveness of the preventive measures used, including any subsequent economic and social changes.

Pellagra

Although pellagra has almost disappeared from such areas as the South Eastern United States of America as a result of a combination of public health measures and the raising of socio-economic levels, it is still to be found in Egypt, Yugoslavia and some parts of Africa where corn (maize) supplies more than 60 per cent of the daily calories. As has been shown in the U.S.A., pellagra will disappear with the changes in the dietary pattern which usually follow changes in agricultural policy and economic development. Between 1950 and 1956 WHO consultants made surveys in Egypt, Yugoslavia and Basutoland which indicated the extent of the problem, and measures for control and prevention. In Yugoslavia, it has been demonstrated that the enrichment of maize with niacin and other B vitamins in rural areas is effective in reducing incidence, and preventing recurrence of the disease. A WHO team in Basutoland is assisting the government in its programme for the eradication of pellagra, the main deficiency disease in that country.

Beri-Beri

This is the chief nutritional deficiency disease of the rice-eating populations and is on the increase again in areas where small power-driven mills have replaced hand mills, and highly milled rice low in vitamin B₁ has therefore replaced under-milled rice. Additional losses of vitamins occur through frequent washing of the rice and discarding of the water. In the adult beri-beri is a much more important cause of morbidity than of mortality. On the other hand there is evidence that in vitamin B-depleted populations the disease may cause very high infantile mortality rates.

Assistance has been given to the governments of Burma and Thailand in surveying the problem and working out preventive measures. These may be short term, based on the wide use of the cheap synthetic product, and/or long term educational measures to change the dietary pattern.

Hypovitaminosis A

This is a common condition in a number of countries in South East Asia, and is also to be found in Africa. It is particularly severe in Indonesia where 1-3 per cent of pre-school age children in Central Java are said to be severely affected. In this country this deficiency is responsible for much blindness and many deaths, and its severity is surprising in the tropical rain belt where supplies of carotene are abundant. A study has already been made in Indonesia which has

shown the frequent association of hypovitaminosis A with protein malnutrition. This investigation showed that green leaf vegetables were consumed, and suggests that because of the associated deficiency, vitamin A could not be obtained from the precursor—carotene. Further research into this disease is now being planned.

Anaemia

Anaemia is a public health problem of considerable importance in the under-developed and tropical parts of the world. Where it is severe it is probably responsible for many maternal deaths. It also impairs health and working capacity and leads to economic loss. Iron deficiency anaemia is generally much the most common form of the disease.

In most tropical countries the dietary intake of iron is equal to, or greater, than that accepted as adequate for Europe and North America. Interference with absorption may be one of the causes of this form of anaemia. This may be due to chronic diarrhoeal conditions, and other infections, or the bulky carbohydrate diets which although rich in iron have high phosphate and phytate and low calcium levels. Chronic protein deficiency may also be a factor in the aetiology and, of course, heavy infestation with hookworm plays an important part in many areas. There is some evidence that iron lost in sweat and sweat-contained cells, may be many times greater in the tropics than in the temperate zones.

WHO has carried out extensive studies in two different countries and has made grants to investigators working on this problem. Towards the end of 1958 a study group was convened on iron deficiency anaemias and arrangements are now being made to embark on a much more extensive research programme.

Nutrition and Infection

A disease problem which has not received adequate attention is the effect of the association of communicable disease and malnutrition. In countries where the general infant and child mortality rates are high, there is an excessively high case mortality from common infectious disease such as measles and bacillary dysentery. In more privileged populations these infections are not ordinarily fatal.

The nutritional state of the host may determine the incidence, progress and severity of communicable disease. On the other hand infections often precipitate such serious disorders as kwashiorkor, keratomalacia and beri-beri. Field studies suggest that the high

infant and child mortality in tropical and technically under-developed countries is accounted for either by infections which would not ordinarily be fatal in well nourished populations, or by nutritional disease such as kwashiorkor and marasmus classified by village officials as "worms" or dysentery. It is clearly of great public importance to establish the full significance of this relationship, and a carefully planned extensive field experiment is now being embarked upon by the Institute of Nutrition of Central America and Panama. WHO was able to give a grant to facilitate the preliminary investigations.

Degenerative Heart Diseases

Although the main attention and efforts of WHO in the field of nutrition have been, and still are, centred in the developing countries where the diseases described above are rife, more attention is being given recently to over-nutrition and some of its effects. Following a recommendation of the Joint FAO/WHO Expert Committee in 1954 that the problem of degenerative heart diseases, including coronary occlusion, angina pectoris and myocardial degeneration, should be studied in relation to diet, a study group met in 1955 to review this field and recommend a research programme which should help to clarify some of the major factors involved in the aetiology of those diseases.¹⁸ In 1958 an Expert Committee gave particular attention to classification of diseases and cardiovascular epidemiology,¹⁹ and in 1959 a cardiovascular disease unit was formed within WHO. The Organization is now planning an extensive programme of research in the field of cardiovascular disease. Particular attention will be given to ischaemic heart disease.

Supplementary Feeding

Supplementary feeding programmes developed through the schools and through the maternal and child health centres represent a valuable means of improving the health and nutrition conditions of mothers and of children of various ages, besides being suitable channels for introducing nutrition education. FAO, in co-operation with UNICEF, has devoted great attention to the development of school-feeding programmes in member countries; a standard publication on this subject was produced in 1953,²⁰ and two Regional Seminars on school-feeding were organized in 1958 in South America,²¹ and in Asia and the Far East,²² respectively.

The opportunities for health education offered by the attendance of the mother at Maternal and Child Health Centres are perhaps unique, and because the staff of such centres are in a position to

treat sickness, they are well placed to influence people, particularly the mother.

Education and Training

A common obstacle to the development of adequate programmes for the prevention of nutritional disease is the failure to recognize the nature and importance of the problem. The emphasis in public health in the less developed countries has been on communicable disease and in both undergraduate and postgraduate medical training nutrition has not received sufficient attention. This is equally true in the training of nurses and other personnel associated with nutrition programmes so that even when the disease problem is recognized it is rarely properly investigated and programmes for prevention lack direction and are based on inadequate understanding of basic causes.

FAO and WHO have in the past few years, together with different host countries, organized five courses lasting 2-3 months for physicians, biochemists, agriculturalists and social workers. This is a beginning but it is quite evident that if significant advances in the prevention of malnutrition are to be made education and training will have to receive more attention.

Nutrition Education

While nutritional disease is sometimes due to the unavailability of suitable foods it often results from a failure on the part of the population to use properly what is available. An important means of improvement and alleviation of malnutrition, therefore, is through education. It is well known that to change food habits is difficult, because beliefs about food are generally strongly held. It is also often true that the narrower the range of the foods consumed the more resistance there is to change.

Recent advances in the knowledge of how people learn and what induces them to change long-established habits, have outlined an approach to the problem of nutrition education. Instruction is largely ineffective unless there is a strong desire to learn and people do not readily change their ways unless they recognize the advocated changes as a means to an end which they themselves desire.

That nutrition education based simply on routine advice is not sufficient has been shown in a WHO assisted field study in India. The diets of infants and children in villages, served by health centres whether old or recently established, did not differ from the age-old established pattern.⁸

Studies such as those made by WHO in Guatemala and Indonesia on food practices in the villages, provided information on attitudes towards mortality of children, family instability and sickness—especially protein malnutrition—the influence of adoption and of different treatment of male and female children on the nutritional status of the child. These studies have provided useful background information, of the kind needed for the preparation of a sound educational programme to prevent malnutrition in young children.

In 1955 WHO published a report on Infant Nutrition in the sub-tropics and tropics²³ by a consultant, which provides some general information on weaning practices in different countries, and indicates methods of improving the diets of infants in those areas, based on nutrition education and the use of locally available foods.

A joint FAO/WHO Seminar on Nutrition and Health Education in Baguio (Philippines), held in 1955, devoted much of its time to the ways of improving the technique of nutrition education.²⁴ A similar seminar was held in Germany in 1959.²⁵ Others are planned to be held in Brazil and Mexico.

Teacher training courses in nutrition have been organized in some countries in order to introduce nutrition education in the school curriculum.

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